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OCCURRENCE OF DIABETES MELLITUS IN FAMILIES OF PATIENTS WITH CYSTIC FIBROSIS OF THE PANCREAS

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INTRODUCTION

RECENT investigations of cystic fibrosis of the pancreas have been directed toward further clarification of the pathogenesis and genetic mechanisms responsible for the disease.[1,2] There is increasing evidence that mucoviscidosis is a generalized disease process which is expanding beyond the field of pediatrics to invade the domain of treatment of diseases of adults.[3]

For example, in a study of 262 adult patients with various disorders, Peterson[4] found an abnormally high electrolyte content of sweat in 14 patients. Of these, eight had bronchiectasis, two had chronic bronchitis, two had peptic ulcer, one had chronic calcific pancreatitis, and one had allergic bronchial asthma. Two of the 14 had diabetes mellitus. Koch[5] emphasized the high frequency of peptic ulcer in relatives of patients with mucoviscidosis and suggested a possible relation between the two diseases. Recently Wood and others[6] showed that a significant number of relatives of patients with cystic fibrosis of the pancreas have chronic pulmonary disease and are subject to so-called "asthma." These studies suggest that the heterozygous state may give rise to such clinical manifestations more often than previously suspected.

The purpose of this report is to present data obtained from an analysis of the family histories of 25 cases of cystic fibrosis of the pancreas. In a review of the literature, we were unable to find any information regarding the incidence of diabetes mellitus in relatives of patients with mucoviscidosis. It seemed of interest to point out the high frequency of a positive family history of diabetes found in the group of 25 cases studied by us.

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MATERIAL AND METHODS

The records of 25 patients with a well-established diagnosis of cystic fibrosis of the pancreas seen at the University of Rochester Medical Center during the five-year period 1956 through 1960 were reviewed.

Fifteen patients were males and ten were females. None of the patients were related. The age at which the diagnosis was made was from six weeks to 24 years, the mean being eight years and three months.

In 11 patients clinical criteria plus an abnormally high content of electrolytes in the sweat,[7] low activity of pancreatic enzymes obtained by duodenal intubation, and impaired absorption of vitamin A ester provided the basis for diagnosis. The sodium level of the sweat ranged from 89 meq./L. to 270 meq./L. with a mean value of 150 meq./L. (normal value 70 meq. or less). The sweat chloride varied between 95 and 400 meq./L. with a mean value of 220 meq./L. (normal value 70 meq. or less).

In 14 patients characteristic pancreatic and pulmonary lesions were found at postmortem examination.[8]

RESULTS

Table I summarizes the hereditary features of the 25 patients. Eleven (44 per cent) of the 25 patients with cystic fibrosis of the pancreas had a positive family history of diabetes mellitus. The mothers of three of the patients were known diabetics at the time of delivery. Diabetes mellitus was diagnosed in one father. The other seven cases of diabetes mellitus occurred in grandmothers (4), in grandfathers (2), and in a maternal aunt (1).

TABLE I.

	FAMILY HISTORY OF DISEASE IN:			
	25 PATIENTS WITH CYSTIC FIBROSIS OF THE PANCREAS		25 PATIENTS WITH CELIAC DISEASE	
	NO.	%	NO.	%
Diabetes mellitus	11	44	1	4
Pulmonary disease	9	36	3	12
Duodenal ulcer	2	8	0	0
Cystic fibrosis in siblings	6	24	0	0
Celiac disease in other family members	0	0	4	16

In other relatives of these patients, peptic ulcer was diagnosed in two, and nontuberculous chronic pulmonary diseases (emphysema, chronic bronchitis, pulmonary fibrosis, and bronchiectasis) were present in nine. A history of cystic fibrosis of the pancreas was present in siblings of six of the patients.

To evaluate the significance of the above findings we thought it advisable

to scrutinize the family histories of a group of patients with a somewhat similar chronic disease process occurring at a relatively early age. Accordingly, the records of the last 25 patients with a well-established diagnosis of celiac disease seen at this institution since 1952 were reviewed. Twelve were females and 13 were males. The age at which the diagnosis was made ranged from 3 months to 30 years with a mean of 7 years. Of the 25 patients with celiac disease one had a family history of diabetes mellitus occurring in a maternal grandmother (Table I). Three patients had a family history of asthma. Other members of the family were known to have celiac disease in four instances (a first cousin and maternal uncle of one patient and 3 siblings).

In regard to the incidence of diabetes mellitus in the families of patients with cystic fibrosis, we attempted to make further comparison with a roughly matched sample somewhat more representative of the general population. The records of the first 40 patients under the age of 25 admitted since January, 1958, with the following diagnoses were studied: (1) "Diarrhea of undetermined cause," (2) "Acute bronchitis," (3) "Tonsillectomy and adenoidectomy." The findings are summarized in Table II along with those of the fibrocystic and celiac disease groups. The grandparents of 5 of the 40 patients with diarrhea of undetermined cause had diabetes mellitus. Among the patients with acute bronchitis 4 grandparents and one paternal aunt had diabetes mellitus. Of the patients admitted for tonsillectomy and adenoidectomy, 2 grandparents had diabetes mellitus.

From the total group of 120 patients with relatively common disorders of childhood or youth, a total of 12 relatives (or 10 per cent) with a family history of diabetes were found as compared to 44 per cent in the group with fibrocystic disease.

TABLE II. FAMILY HISTORY OF DIABETES MELLITUS IN THREE GROUPS OF PATIENTS SEEN AT THE STRONG MEMORIAL HOSPITAL, 1958-1959

	CYSTIC FIBROSIS OF THE PANCREAS	CELIAC DISEASE	DIARRHEA OF UNDETERMINED CAUSE	ACUTE BRONCHITIS	TONSILLECTOMY AND ADENOIDECTOMY
Number	25	25	40	40	40
Males	15	12	25	30	18
Females	10	13	15	10	22
Age range	6 weeks to 24 years	3 months to 30 years	1 week to 25 years	6 weeks to 22 years	2 years to 25 years
Mean age	8 years 3 months	7 years	10 years	12 years	16 years
Diabetes in relatives	11	1	5	5	2
Per cent	44	4	12.5	12.5	5

COMMENT

An increased incidence of diabetes mellitus in the relatives of patients with cystic fibrosis of the pancreas has apparently not been previously recorded. However, other disorders in the immediate families have been noted. These include chronic pulmonary diseases[4,9] and peptic ulcer.[5,10] It has been said that related

disease processes and abnormal sweat electrolyte concentrations have been found in 20 to 30 per cent of the immediate families of patients with mucoviscidosis.[3]

The occurrence of diabetes mellitus in patients with cystic fibrosis of the pancreas is apparently low. In a series of 550 patients with cystic fibrosis of the pancreas, di Sant Agnese and Andersen[11] found only 2 patients, 10 and 13 years of age, with diabetes mellitus. Both had pancreatic calcifications. One of the two had a positive family history of diabetes mellitus. These authors speculated that diabetes mellitus with or without pancreatic calcification may be encountered more frequently in cystic fibrosis as, due to improved methods of treatment, the average age of the patients increases. They did not mention the incidence of diabetes mellitus in relatives of patients with mucoviscidosis.

Dolger[12] has had only two patients with both mucoviscidosis and diabetes mellitus in his extensive experience in treating diabetic patients. The mother of one of these patients subsequently developed diabetes mellitus.

In regard to the genetics of diabetes mellitus, Steinberg[13] concluded that the disease is the result of the homozygous state of a single gene and that as many as 5 per cent of the population of the United States are "homozygous for the gene determining susceptibility to diabetes." Lamy and associates,[14] in a study of 500 diabetic patients found a family history of the disease in 6.5 per cent. Sakakida and co-workers[15] reported an incidence of 26 per cent of diabetes mellitus in immediate relatives of 175 diabetics in contrast to its occurrence in only 1.1 per cent of 20,379 control cases.

The explanation for the increased familial incidence of diabetes mellitus in our patients with fibrocystic disease is not clear. It could be a chance finding, but the absence of a similar trend in the cases with celiac disease suggests that it may be significant. Similarly, a less frequent family history of diabetes mellitus was noted in the 3 other "control groups." The exact number of relatives of any of the patients studied could not be ascertained in our investigation as a complete family tree was not available in all cases. However, we believe that the presence of diabetes mellitus in parents, grandparents, and aunts and uncles was adequately questioned in all instances and was probably no more avidly pursued in the fibrocystic than in the other groups. There was no indication that more kindred were available in the fibrocystic group for comparison, and, as parents and grandparents were those primarily concerned, a postulated greater number of uncles and aunts would make little change in the incidence.

A remote possibility is that diabetes mellitus in the relatives of patients with mucoviscidosis could be due to silent involvement of the pancreas. Such a hypothesis would explain the high percentage of cases of diabetes mellitus in the immediate relatives. Further studies using the sweat electrolyte and other appropriate tests may be of value in the investigation of the incidence of diabetes mellitus in "cystic fibrosis families" and in the general population.

Pancreatic disease of a quite different type has been found in association with a high familial incidence of diabetes mellitus. Scholtz and others,[16] from the Mayo Clinic, reported an incidence of 29 per cent of diabetes mellitus in relatives of patients with functioning pancreatic islet cell tumors.

SUMMARY

A family history of diabetes mellitus was found in 11 of 25 patients with cystic fibrosis of the pancreas seen at the University of Rochester Medical Center during a five-year period. The significance and implications of this finding are discussed.

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Gastrointestinal

LOSS OF LIFE DUE TO CIRRHOSIS OF THE LIVER: CALIFORNIA

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EARLY in 1955, the California State Department of Public Health began studies dealing with selected facets of the alcoholism problem. Among them was a 12 to 18 month follow-up study of 680 alcoholics—individuals under treatment or commitment because of their excessive drinking problems—who began treatment in 1954 in three selected treatment facilities.[1]

Several findings emerged from this first follow-up study: (1) mortality among the alcoholics studied was at least two to three times greater than expected in a population of comparable age, sex, and race, and (2) alcoholics die of the same wide diversity of conditions which cause death among the general population.

These two findings led to a series of investigations designed to describe and measure alcoholism and related mortality in California. One such investigation dealt with mortality due to all types of cirrhosis of the liver in California—not necessarily from alcoholism alone. Some of the results of this investigation are reported here.

BACKGROUND

The number of deaths from cirrhosis of the liver has increased in the last 30 years, while deaths from other formerly prominent causes have declined. Today, cirrhosis is the tenth leading cause of death in the United States.[2] In California, cirrhosis of the liver was the eighth leading cause of death in 1957.[3] It was fifth in San Francisco for the same year, with the crude death rate of 47.3 per 100,000.[4]

Recent figures reveal that among the industrial policyholders of the Metropolitan Life Insurance Company, mortality from cirrhosis of the liver has increased steadily during the past 8 years.[5] In spite of a frequently voiced reluctance to use cirrhosis of the liver as a cause of death for insurance claims, deaths due to this disease ranked seventh in amounts disbursed in death benefits ($7,793,000) by the Metropolitan Life Insurance Company in 1957.[6]

Cause of death ranking is usually based on crude death rates and, therefore, does not fully reveal the seriousness of cirrhosis of the liver as a public health problem. To appraise adequately the loss to society from various causes of death, judgment cannot be made solely by comparing cause-specific death rates. Other measures, such as diminished life expectancy and loss of potential life-years should be examined. A large proportion of people who die of major chronic diseases (heart disease, cancer, and vascular lesions of the central nervous system) are aged 65 or over. However, an examination of mortality data on cirrhosis of the liver for the 3 year period, 1949-1951, disclosed that 72 per cent of those dying from cirrhosis of the liver in California were in the most productive period of life (35-64 years).[7] The death of an individual during his most productive years represents a greater loss to society than his death in later years.

As Fig. 1 shows, the age-adjusted death rate for cirrhosis of the liver declined from around 17 per 100,000 in 1910 to 8 per 100,000 in 1920; by 1957 it had more than doubled the 1920 rate. In California in 1957, 2,453 deaths were due to cirrhosis of the liver, a crude death rate of 17.3 per 100,000 population. Among those 45-54 years of age, deaths from cirrhosis for both sexes were exceeded only by heart diseases and malignant neoplasms. Moreover, cirrhosis ranked sixth as a cause of death in the age group 35-44 years, and fourth in the group 55 through 64 years old.

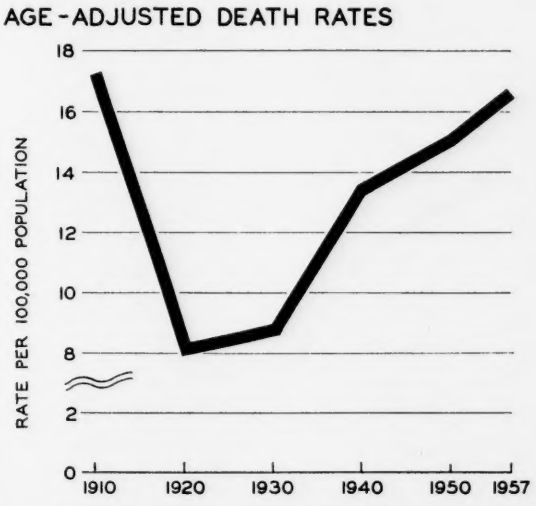

Fig. 1.—Mortality rate from cirrhosis of the liver in California, 1910-1957. Note: Adjustment was by the indirect method using United States 1940 rates as the standard. Rates for 1910-1940 were adjusted for changes in the International Statistical Classification by application of a comparability ratio. (State of California, Department of Public Health, Division of Alcoholic Rehabilitation, November, 1958.)

It is the purpose of the present investigation to illustrate by means of life tables: (1) the gain in the average life expectancy at any age if cirrhosis of the liver as a cause of death could be eliminated, (2) the potential years of life lost due to this cause, and (3) the years of "maximal productive life" lost due to cirrhosis of the liver as compared with other leading causes of death.

STUDY METHODS

If cirrhosis of the liver were eliminated as a cause of death, how much would be added to life expectancy? To answer this question, life tables were constructed for white males in California showing (1) death from all causes, and (2) death from all causes excepting cirrhosis of the liver.

A mortality table such as the one constructed in this study eliminates a cause of death, thereby assuming that there were no deaths from the omitted cause. This method is called the "zero mortality assumption," and calculations based on it show the increased life expectancy resulting from eliminating deaths from a particular cause.

This procedure was first suggested in 1760 by David Bernoulli in connection with the controversy over the use of inoculation for smallpox. D'Alembert (1760) and Trembley (1796) further developed the method, and Duvillard (1806) calculated the increase in life expectancy which would result from the elimination of smallpox. More recently, various workers[8-13] have discussed the use of life tables to illustrate similar principles. In order to calculate the gain in life expectancy, life tables based on deaths from all causes were compared with tables which use the zero mortality assumption for cirrhosis of the liver.

In calculating these tables, it was assumed that mortality from cirrhosis of the liver is nonselective, that is, that after the removal of cirrhosis as a cause of death, the population is still considered subject to the mortality rate for all causes of death except the cause eliminated. For example, for white males in the age group 45-49 years during the years 1949-1951, there was an average of 2,817 deaths due to all causes, of which 170 deaths were due to cirrhosis of the liver. When cirrhosis was eliminated as a cause of death, the 170 "saved" lives were assumed to be subject to the same risk of death as the remaining population. This resulted in 1.4 deaths which were added to the 2,647 lives lost to other causes of death, and a new age-specific death rate was calculated.

Greville's method of abridged life table construction[11] was used to derive the probability of dying within a certain period from the annual age-specific death rates adjusted as described.

Sources of Data.—Calculations for two of the measures discussed in this paper (gain in life expectancy and potential life-years lost) are based on life tables of California white males. In order to eliminate the possibility of an unusual fluctuation in deaths for any one year, deaths for the 3 years, 1949-1951, compiled from the death records of the California State Department of Public Health, were averaged.[7] This procedure was followed throughout for deaths referable to the 1950 census. Life tables were constructed using 1950 census data for California.[14] The Bureau of the Census lists population in 5-year age groups up to 75 years of age, followed by a 10-year age group, 75-84 years, and a group 85 years of age and over. These age groups for white males were used in constructing abridged life tables.

The section on the maximal productive life-years lost to specific causes of death in California is based on the California Life Table for 1950 published by the National Office of Vital Statistics.[15] At the time of this study, the latest mortality

statistics available were for 1957, the year reported here. Computations were based on the total population and data were taken from the 1957 Vital Statistics Report of the California State Department of Public Health.[3]

RESULTS

If it were possible to eliminate cirrhosis of the liver as a cause of death, the average length of life of white males in California would be increased by 0.31 years at birth. Table I shows the increase in life expectancy at the other ages. The gain in life expectancy from the elimination of a single cause of death is distributed over the entire population, which tends to make the percentage increase very slight. But when one considers that three tenths of a year is added on an average to the life of each individual in the life table cohort, the gain is considerable.

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TABLE I. AVERAGE LIFE EXPECTANCY AND THE YEARS OF LIFE THAT WOULD BE GAINED BY ELIMINATING CIRRHOSIS OF THE LIVER AS A CAUSE OF DEATH FOR WHITE MALES, CALIFORNIA, 1949-1951

AGE GROUP (YEARS)	AVERAGE LIFE EXPECTANCY AT MID-POINT AGE OF INTERVAL (YEARS)	IF DEATHS FROM CIRRHOSIS OF THE LIVER (ISC 581) WERE ELIMINATED	
		YEARS	GAIN
0–4*	65.83	66.14	.31
5–9	63.27	63.58	.31
10–14	58.47	58.78	.31
15–19	53.66	53.97	.31
20–24	49.02	49.34	.32
25–29	44.47	44.80	.33
30–34	39.85	40.17	.32
35–39	35.24	35.56	.32
40–44	30.77	31.06	.29
45–49	26.52	26.77	.25
50–54	22.59	22.79	.20
55–59	19.01	19.15	.14
60–64	15.75	15.85	.10
65–69	12.83	12.90	.07
70–74	10.27	10.31	.04
75–84	8.11	8.14	.03
85+	4.77	4.78	.01

Note: Numbers in parentheses are Sixth Revision International List Numbers.
Source: References 7 and 14 and original life-tables computed by the authors.
*In the construction of abridged life-tables, it is usual to separate the first 5 years of life into the age groups 0, 1, and 2-4 years. Since there are few deaths from cirrhosis at these ages, one combined 5-year age group was used.

Potential Life-Years Lost Because of Cirrhosis.—To show further the seriousness of cirrhosis as a cause of death, the potential life-years lost because of it have been calculated for California white males. Greville's procedure was followed, which computes life expectancy from special life tables calculated with the cause of death under study eliminated.[16] The tables calculated assume zero mortality

from cirrhosis of the liver. The assumption is that if it were possible to prevent deaths from this cause in one year, such deaths could be eliminated in subsequent years as well. This has the effect of increasing life expectancy. This method incorporates the age at death into the measure of the potential loss to society resulting from these causes of death. The life-years lost are not felt in the calendar year in which they occur, but over a period of many future calendar years. Such a computation assumes that mortality conditions of the year of computation remain constant.

TABLE II. POTENTIAL LIFE-YEARS LOST TO CIRRHOSIS OF THE LIVER FOR WHITE MALES, CALIFORNIA, 1949-1951

AGE GROUP (YEARS)	LIFE EXPECTANCY IF DEATHS FROM CIRRHOSIS OF THE LIVER (ISC 581) WERE ELIMINATED (YEARS)	ADJUSTED* NO. OF DEATHS DUE TO CIRRHOSIS OF THE LIVER	LIFE LOST BECAUSE OF CIRRHOSIS OF THE LIVER (YEARS)
0–4†	66.14	2.98	197.10
5–9	63.58	1.00	63.58
10–14	58.78	1.00	58.78
15–19	53.97	1.00	53.97
20–24	49.34	1.00	49.34
25–29	44.80	8.98	402.30
30–34	40.17	25.95	1,042.41
35–39	35.56	74.77	2,658.82
40–44	31.06	122.39	3,801.43
45–49	26.77	168.60	4,513.42
50–54	22.79	172.72	3,936.29
55–59	19.15	150.02	2,872.88
60–64	15.85	127.24	2,016.75
65–69	12.90	123.62	1,594.70
70–74	10.31	65.70	677.37
75–84	8.14	54.69	455.18
85+	4.78	6.33	30.26
Total years of life lost because of cirrhosis of the liver (3 year average)			24,414.58

Note: Numbers in parentheses are Sixth Revision International List Numbers.
Source: References 7 and 14 and original life-tables computed by the authors.
*Number of deaths were adjusted by assuming the "saved" lives to be subject to the mortality rate for all other causes.
†In the construction of abridged life-tables, it is usual to separate the first 5 years of life into the age groups 0, 1, and 2-4 years. Since there are few cirrhosis deaths at these ages, one combined 5-year group was used.

The number of potential life-years lost to cirrhosis of the liver is obtained by multiplying the number of adjusted deaths from this cause by life expectancy at the age of death, and then adding the products for all ages. The adjusted deaths result when the "saved" lives are subject to the mortality rate for all other causes. Table II reveals a loss of 24,415 potential life-years to cirrhosis of the liver for white males. The magnitude of these figures illustrates the many years of life sacrificed to this cause of death. Since the number of deaths from cirrhosis of the

liver in California is presently more than double the number on which these calculations are based, the annual number of potential life-years lost to cirrhosis is considerably higher than Table II indicates.

Maximal Productive Life Years Lost.—Although some people contribute a great deal to society before age 35, the average individual has his greatest period of productivity after the age of 35. Many nonprofessional people enter the working force between 18 and 25 years of age, whereas preparation for and establishment of occupational or professional roles require approximately the first 25 years of life. However, it is not until around the age of 35 that plans for productivity are settled or "fixed" for the average individual. The authors are herein focusing attention on what we call the "maximal productive period," beginning at age 35, and taking 65 years of age as the cut-off point because this is the usual retirement age.

Cause of death rankings assign a weight of one to each death. There were 2,453 deaths due to cirrhosis of the liver in California in 1957 and, under the usual rating system, cirrhosis ranked eighth. However, analyzing mortality by merely counting deaths does not take into account the greater importance of death at certain ages. For example, more significance should be attached to a cause of death which reduces life during the period of greatest productivity than to causes which take their toll at advanced ages. Various analysts[11,13,17] have introduced weighting systems which attach more importance to death at specific ages. The conventional method of ranking causes of death emphasized those causes of death which are responsible for the greatest number of deaths. By limiting the "maximal productive period" to the ages of 35-64 years, we are placing more importance on a death at these ages. The majority of deaths from cirrhosis of the liver occur during this period of greatest productivity and, as Table IV indicates, in 1957, for the three decades of 35 through 64 years of age, cirrhosis of the liver caused the third greatest number of deaths in California.

Table II considers the loss to society of a death due to cirrhosis at any age. Based on life expectancy, the death, for example, of a 5-year-old child would result in a loss of around 63 years of "potential life-years." However, calculations for Table IV do not give credit to the 5-year-old because society has not yet trained him for productive labor. Many, 20 or 25 years old, do productive work but, in Table III, we are attempting to measure only the period of maximum productive labor. Thus, in the calculations of Table IV only a death between the ages of 35 to 65 gets credit for loss of "maximal productive life-years," since such a death represents the loss of a fully trained member of society during the peak of his productive effort. Our calculations of the maximal productive life-years lost for California are based on the year 1957 and both males and females are considered in the calculations.

Although persons at 35 years of age and persons at the age of, say, 55, may both, on the average, be expected to reach age 65, the chance of doing so is better for those who are 55 years of age. Therefore, when a person dies at the age of 35, the number of maximal productive life-years lost cannot be determined by merely taking the difference between the age of 35 and the limit of 65. Instead, values have been computed based on the life table function (T_x) which is the

total number of years lived by the stationary population of the life table after a certain age, in this case, between the age of death and age 65. This summation is divided by the number of persons (l_x) reaching this exact age in the life table. The latest National Office of Vital Statistics life table for California, that of 1949-1951,[15] was used and computations were made for the mid-point age of each interval (Table III).

TABLE III

AGE	MID-POINT OF INTERVAL	EXPECTATION OF MAXIMAL PRODUCTIVE LIFE YEARS AT MID-POINT AGE OF INTERVAL
35–39	37.5	24.33
40–44	42.5	19.78
45–49	47.5	15.39
50–54	52.5	11.11
55–59	57.5	6.86
60–64	62.5	2.41

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Use of the mid-point age assumes that deaths are spread evenly throughout each age interval. The weighting factor was multiplied by the number of deaths due to each cause within each 5-year age group, and the products were summed to determine the total maximal productive life-years lost to each cause for the ages 35-64.

Table IV shows, for the total population, the number and percentages of all deaths and the crude death rates; and, for ages 35 to 64, the number and percentage of the maximal productive life-years lost to the causes of death which constitute 87 per cent of all deaths in California. The remaining 13 per cent have been combined and are shown as "All Other Causes." It can be seen that, although cirrhosis of the liver ranks eighth according to crude death rates, it takes the third largest toll of life-years during the three decades, 35 to 65 years. Had calculations been based on the ages of 25 to 65 years, the great number of accidents which occur among young males would have shifted the rankings to place accidents ahead of cirrhosis of the liver. However, when similar calculations are restricted to females between the ages of 25 and 65 years, it is found that cirrhosis of the liver ranks third in years of lost life behind diseases of the heart and malignant neoplasms.

The crude death rate for diseases of the heart is nineteen times that of cirrhosis of the liver, whereas the number of maximal productive life-years lost (ages 35-64) to heart disease in 1957 is only about five times that of cirrhosis. The crude death rate for malignant neoplasms is eight times greater than that for cirrhosis, but the maximal productive life-years lost are only four times as great. Vascular lesions of the central nervous system—the third leading cause of death—has a crude death rate of over five and one-half times that of cirrhosis of the liver, but the latter is responsible for more lost maximal productive life-years. Fig. 2 shows the percentage distribution of the number of deaths (all ages)

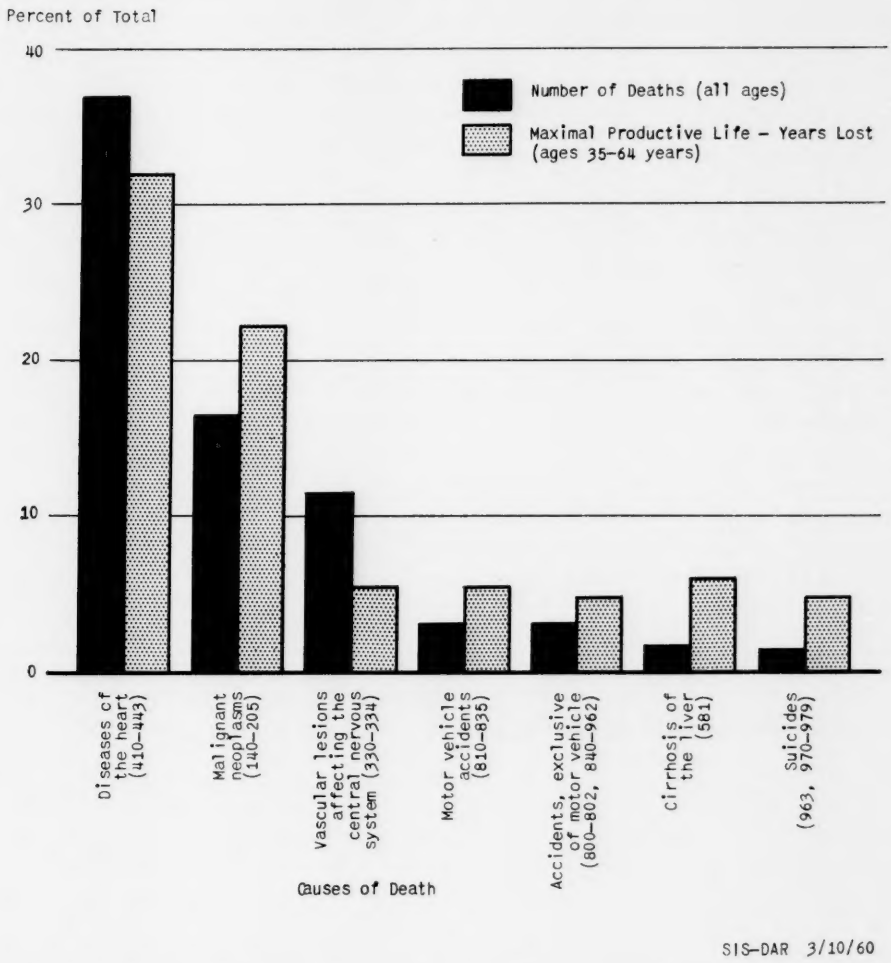

Fig. 2.—Percentage distributions of the number of deaths and the maximal productive life-years lost for seven selected causes of death (California, 1957). (Adapted from California Public Health Statistical Report, 1957.[3])

and the maximal productive life-years lost (ages 35-64) to the seven causes of death with the greatest number of years lost during this period in California. Aside from certain diseases of early infancy, the two causes of death in 1957 which ranked ahead of cirrhosis of the liver but are not shown in Fig. 2, namely, influenza and pneumonia, and hypertension without mention of heart and general arteriosclerosis took 7,961 lives—more than three times that of cirrhosis. When maximal productive life-years (ages 35-64) are examined, it is found that cirrhosis of the liver is responsible for over 9,000 more lost years than the two aforementioned causes combined. The causes of death shown in Fig. 2 account for three fourths of all deaths and over 90 per cent of the maximal productive life-years lost.

TABLE IV. NUMBER OF DEATHS AND CRUDE DEATH RATES, ALL AGES, AND THE NUMBER OF MAXIMAL PRODUCTIVE LIFE-YEARS LOST, AGES 35-64, BY SELECTED CAUSES OF DEATH, CALIFORNIA, 1957

CAUSE OF DEATH	ALL DEATHS (ALL AGES)		CRUDE DEATH RATE	MAXIMAL PRODUCTIVE LIFE-YEARS LOST (AGES 35-64)	
	NUMBER	PER CENT		NUMBER	PER CENT
Total, all causes	123,940	100.0	873.4	370,174	100.0
Diseases of the heart (410-443)	45,869	37.0	323.2	117,761	31.8
Malignant neoplasms (140-205)	20,297	16.4	143.0	81,981	22.1
Cirrhosis of the liver (581)	2,453	1.9	17.3	21,703	5.9
Motor vehicle accidents (E810-E835)	3,875	3.1	27.3	20,030	5.4
Vascular lesions affecting the central nervous system (330-334)	13,971	11.3	98.5	20,028	5.4
Accidents, exclusive of motor vehicle (E800-E802, E840-E962)	3,862	3.1	27.2	17,712	4.8
Suicides (E963, E970-E979)	2,065	1.7	14.6	17,613	4.8
Pneumonia, all forms and influenza (480-493)	4,218	3.4	29.7	9,790	2.6
Tuberculosis, all forms (001-019)	905	0.7	6.4	5,494	1.5
Diseases of the respiratory system (470-475, 500-527)	2,139	1.7	15.1	4,864	1.3
Diabetes mellitus (260)	1,429	1.2	10.1	4,146	1.1
Homicides and war injuries (E964-E965, E980-E999)	552	0.4	3.9	3,932	1.1
Ulcers of the stomach and duodenum (540-541)	976	0.8	6.9	3,723	1.0
Nephritis, chronic and unspecified (592-594)	748	0.6	5.3	3,333	0.9
Infective and parasitic diseases, other than tuberculosis (020-138)	738	0.6	5.2	2,902	0.8
Hypertension without mention of heart, and general arteriosclerosis (444-450)	3,743	3.0	26.3	2,853	0.8
All other causes (residual)	16,100	13.0	113.5	32,309	8.7

Note: Rates are per 100,000 total population estimated in June, 1958, by the State of California, Department of Finance, as 14,190,000 on July 1, 1957. Per cents are rounded independently and may not add to totals. Numbers in parentheses are Sixth Revision International List Numbers.
Source: Reference 3 and computation by the authors.

It can be seen from the chart that the percentage of the number of lives lost is greater than the percentage of the number of maximal productive years lost for diseases of the heart and vascular lesions of the central nervous system, whereas the reverse is true for the other five causes of death shown. The greatest difference between the two measures is that for cirrhosis of the liver, with suicide showing the next greatest difference.

SUMMARY AND CONCLUSIONS

Three measures of loss of life (two of them based on zero mortality tables)

were applied to deaths from cirrhosis of the liver in California. They take into account the factor of age at death, and may be used to gauge the loss to society due to cirrhosis of the liver as a cause of death. Cirrhosis of the liver has become increasingly important in the United States and in California, and is one of the leading public health problems.

The findings showed that the life expectancy for white males in California would be increased 0.31 of a year at birth, if deaths attributable to cirrhosis of the liver were eliminated. During the 3 years, 1949-1951, California white males lost a yearly average of 24,415 potential life-years to cirrhosis of the liver. With California's rapid increase in population, steady improvement in life expectancy and a rising cirrhosis death rate, the future loss of potential life-years due to cirrhosis of the liver will be even higher.

One measure which strikingly points out the importance of cirrhosis of the liver as a public health problem is the loss of maximal productive life-years. During the age span of 35-64 years, cirrhosis is responsible for many lost years of life. Although cirrhosis causes only 1.9 per cent of all deaths, 5.9 per cent of the maximal productive life-years lost (ages 35-64) are due to cirrhosis. By use of this measure, loss of maximal productive life years, the social cost of deaths due to cirrhosis is brought into sharper focus and perspective in relation to other causes of death.

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Epidemiology

THE EPIDEMIOLOGY OF SECONDARY AMENORRHEA

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FOLK-KNOWLEDGE has insisted throughout history that emotional "shocks" affect menstrual cycles. Perhaps because of the universality of this belief little has been done to document accurately the phenomenon by those concerned with medical science. It is the purpose of this paper to examine such facts as are available, interrelating psychic function and menstrual aberrations, and to evaluate these facts endocrinologically, psychologically, and sociologically in the light of present knowledge.

EPIDEMIOLOGIC CONSIDERATIONS

Secondary amenorrhea, defined here as the cessation of menstrual bleeding after the menarche for any period of time exceeding 2 months, and not due to pregnancy, is such a familiar symptom under some circumstances that it has been regarded as commonplace and consequently received little study. Physicians of universities and nursing schools expect that in a small percentage of their freshman class there will be girls who cease menstruating on admission only to resume periods at Christmas or Easter holidays. These girls require no treatment except reassurance, and indeed do not respond uniformly if endocrine treatment is given.[43] Usually they have no further menstrual difficulties.

In spite of this widespread knowledge, the rates have not been well documented. Most studies include data on other menstrual disturbances arising under similar circumstances, especially oligomenorrhea and, to a lesser extent, menorrhagia. Unless indicated to the contrary, we have separated amenorrhea from the others to simplify an epidemiologic survey. It is, however, by far the most common derangement.

The present study began as an epidemiologic review. As the facts unfolded, it became obvious that both new data and new evaluations were needed. We

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therefore began a study of students in a women's college in Pittsburgh (Chatham) and at the same time expanded our original review to include endocrine and psychiatric material. Fig. 1 encompases the rates described in the literature as well as our own findings. The details explaining these will be described in an order generally following the ascension of the rates. In the strict epidemiologic sense, such rates, while comparable to each other, fall into a category without a name since they indicate neither prevalence nor incidence. In effect, they show frequency of occurrence proportionate to the population at risk at the time of study.

It seems fair to assume that many reported rates would be lower than actual occurrence since they depend on a "complaint" of amenorrhea and may exclude those girls fearing pregnancy or fearing being accused of pregnancy. This applies especially to rates in the lower range.

Marwil[27] has reported that in Wave inductees the rate of amenorrhea was 2 per cent (100 out of 5,000) and he comments that "the transient disturbing element of recent entrance into the Navy with its discipline, nostalgia for home, and rigors of a training school contribute to an effect on the psyche."

In a study of psychiatric cases, Strachan and Skottowe[37] used 1,000 gynecologic patients as controls and their rate of amenorrhea was 1.9 per cent. More pertinently, Westman[41] asked 2,262 normal pregnant women in an obstetric clinic whether they had ever had amenorrhea in the past. While these data are, of course, not comparable with the others as a "rate" since they cover a 10 year period, the data are nevertheless of great interest as an indication of symptom frequency. Of the women questioned, 7.7 per cent had had such an episode, in 80 per cent of whom it had disappeared spontaneously, whereas the remaining 20 per cent resumed normal periods with hormone treatment. Westman's subjects offered a variety of explanations for the precipitation of the amenorrhea (Table I).

TABLE I

	DURATION OF AMENORRHEA		
	6 MO.	6-12 MO.	12 MO.
Environmental	26	8	–
Childbirth	2	1	11
Nervous disease	10	2	2
War amenorrhea	1	2	2
Disorder of stomach	3	1	2
Disorder of thyroid	1	–	3
Diabetes	–	–	2
Miscellaneous	2	3	1

Our student data indicated that among the freshman class the rate was 4.9 per cent (8 of 170 freshmen), while the over-all student rate in all classes was 2.3 per cent (12 of 500). These rates were first determined by asking the nurse how many students had presented to the infirmary with the complaint of amenorrhea.

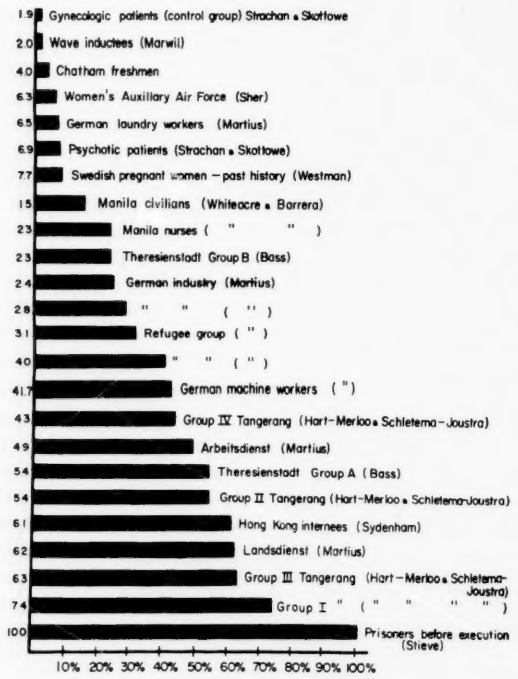
1.9 Gynecologic patients (control group) Strachan & Skottowe
2.0 Wave inductees (Marwil)
4.0 Chatham freshmen
6.3 Women's Auxiliary Air Force (Sher)
6.5 German laundry workers (Martius)
6.9 Psychotic patients (Strachan & Skottowe)
7.7 Swedish pregnant women — past history (Westman)
15 Manila civilians (Whiteacre & Barrera)
23 Manila nurses (" ")
23 Theresienstadt Group B (Bass)
24 German industry (Martius)
28 " " (")
31 Refugee group (")
40 " " (")
41.7 German machine workers (")
43 Group IV Tangerang (Hart-Merloo & Schletema-Joustra)
49 Arbeitsdienst (Martius)
54 Theresienstadt Group A (Bass)
54 Group II Tangerang (Hart-Merloo & Schletema-Joustra)
61 Hong Kong internees (Sydenham)
62 Landsdienst (Martius)
63 Group III Tangerang (Hart-Merloo & Schletema-Joustra)
74 Group I " (" " " ")
100 Prisoners before execution (Stieve)
10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Fig. 1.—Prevalence rates per 100 for secondary amenorrhea in specified groups of women. (From Loeser.[23])

Subsequently, she made a check of the total student body and a number of additional cases were discovered; some of the girls had attached no particular importance to the symptom and thus had not reported it. Whether this further check included or excluded any girls fearing pregnancy we cannot say.

Sher,[36] studying women in the British Auxilliary Air Force during the war years, found that in 3 consecutive years (1941-1943), the annual frequency in new recruits varied only from 6.2 to 6.4 per cent. This included a total of 1,727 women; 44.6 per cent of these had a menstrual delay of 3 months, 20.9 per cent of 2 months, only 2.2 per cent of 7 or more months. In 1940, in a much smaller group (186 women) the rate was 2.7 per cent. He does not discuss whether this apparent inconsistency in rates was, in his opinion, due to better case finding in the next 3 years or worse wartime conditions. He could not correlate these cases with previous diet or with occupation.

Thus, from all these sources of information, we can presume that, among a group of healthy young women, between 2 to 7 per cent will experience one episode of amenorrhea. It is unlikely that at any one time any group would have a higher prevalence rate than 5 to 6 per cent, but it is also unlikely that it would be lower than 2 per cent.

The older literature describes the coexistence of amenorrhea with other diseases, especially tuberculosis.[31] It was said that often amenorrhea was the first symptom. However, a check made in a modern tuberculosis hospital indi-

cates that under present circumstances there is no amenorrhea among their inpatients. These data are presumed accurate since the supervising nurses are ordered to keep records so that early pregnancy can be detected.[25]

The psychiatric literature discusses secondary amenorrhea as a concomitant of psychosis,[31] and in early writings it was looked upon as a prognostic ill omen. Gregory[10] in his excellent review refers to Hansa who "noted that amenorrhea usually occurred shortly after the onset of the illness and chiefly in patients in whom there were strong affective tensions, such as fear and anxiety. Resumption of menstruation occurred both with improvement in the mental condition and also in patients who became chronic psychotics. As a rule he found patients with normal cycles to show an absence of strong affective disturbance." Strachan and Skottowe[37] compared 250 psychotic patients with 1,000 gynecologic patients and found that among the psychotic women the rate was 5.8 per cent as compared with 1.9 per cent in the controls. They, too, commented on the greater frequency of all menstrual disorders among affective disorders: 35 per cent among manic depressive patients, 25 per cent among schizophrenic patients, 13 per cent among paranoid patients. Without exception the menstrual cycles became apparently normal when the psychiatric disturbance was ameliorated. Ripley and Papanicolau[35] studied vaginal smears during the menstrual cycles of patients with schizophrenic and manic depressive psychoses. They do not give prevalence rates of amenorrhea among their 221 patients, but stated that "a tendency to a delay, a weakened expression or a temporary suppression of follicular reaction was noted. Prolongation of the menstrual interval or amenorrhea was frequent. . . . A correlation between severity of illness and degree of abnormality of menstrual cycle was found."

In the past three decades a new type of data has appeared. It arose from observations of normal women exposed to the highly abnormal conditions of war, flight, or internment. Isolated data from Germany, Indonesia, Manila, and France suggest that much must have been known but not published. Decourt and Michard,[5] in discussing psychogenic amenorrhea, cite many histories of women in whom wartime circumstances could be related directly to the precipitation of amenorrhea. They assume that this knowledge is widespread, but give no rates. Many women who were in camps or were refugees spoke of amenorrhea as a fact of life under such circumstances. One young Dutch woman, interned in Indonesia with her sister, a physician, was told by the latter that of course menstruation would stop, that this was common knowledge in prisons as well.

Many publications reveal a clear effort to differentiate between malnutrition amenorrhea and psychogenic amenorrhea. Keys and his associates,[19] on the basis of all available published data, concluded that, although severe starvation of a fatal nature results in ovarian and uterine atrophy, moderate malnutrition may not do so. Sydenham,[39] reporting from Hong Kong, emphasized that she had never seen amenorrhea in a Chinese woman, no matter how malnourished. She added, however, that this may differ from wartime conditions in that their semi-starvation is a chronic state lasting a lifetime. There is certainly little doubt that extreme degrees of starvation due to severe debilitating illnesses or wartime conditions, are usually accompanied by amenorrhea. The relative influence and

extent to which the menstrual aberrations were due to the malnutrition or anxiety in either set of circumstances was impossible to assess. Martius,[26] for example, reports that in Auschwitz no pads were needed—but this can hardly be described as an effect of starvation alone.

More pertinent are the reports which reveal a relation between stress and amenorrhea before the development of malnutrition. Whiteacre and Barrera[42] noted a rate of 14.8 per cent in women interned in the Santo Tomas Internment Camp in Manila. The rate corrected for age was considerably higher (23 per cent) in the 60 interned nurses who had come to the camp after the seiges of Bataan and Corregidor. Both groups became amenorrheic before becoming malnourished. Martius[26] in a paper significantly entitled "Fluchtamenorrhöe," reported his own studies of several groups of German women under varying circumstances as well as data obtained through personal communication with colleagues elsewhere. The rates are all included in Fig. 1 but a list is included here for simplification of discussion.

Laundry workers	6.5 per cent
Iron workers	24.1 per cent
Munitions workers	28.4 per cent
Machine workers	41.7 per cent
Danish refugees	40.0 per cent
Other refugees	31.0 per cent
Arbeitsdienst	49.2 per cent
Landsdienst	62.3 per cent

He noted marked differences in the incidence or amenorrhea among various groups of women and offered some explanations to account for these. For instance, while the four groups of workers were away from home living in barracks, all except the group of laundry workers were in "camp barracks" where facilities and living conditions were considerably worse. The Arbeitsdienst and Landsdienst were young women 19 to 25 years old who spent one year working on farms (Landsdienst) or in industry (Arbeitsdienst) in order to be allowed subsequently to pursue higher education. They were intellectually superior to and younger than the workers groups and in most cases from better homes. Their working year consisted of quite hard physical labor, living in barracks (Arbeitsdienst) or alone in a farm family of strangers (Landsdienst). The author also noted that as the war neared its end, women, who in spite of decreasing food supply and increasing bombings had retained their periods, became amenorrheic as soon as they fled from their homes.

The Arbeitsdienst and Landsdienst groups were also studied by Kaufmann and Müller[16] who saw these girls when they came to the clinic because of their amenorrhea. Since the total number of students in the groups were not reported, the frequency rates could not be derived. The main interest of the study was in prognosis. The authors found that the average duration of amenorrhea was 8 to 9 months in a group of 790 women, 19 to 20 years of age, who were studied for a period of 2 years. The symptom persisted 4 to 6 months in 30 per cent of the group, 7 to 12 months in 60 per cent, and 13 or more months in 10 per cent.

The average age of menarche in the group menstruating regularly throughout their service was 13.4 ± 0.07 years as compared with 14.2 ± 0.08 years for those who became amenorrheic. This difference was statistically significant.

Sydenham[39] reported that among 324 women interned in Hong Kong, 61 per cent became amenorrheic. She emphasized that in most instances this preceded the malnutrition of camp life, and even within the camp was sometimes associated with weight gain, especially in the younger women. She described a resumption of menstruation in most internees when the meat ration was increased and the development of amenorrhea again when the ration was eliminated. Six subjects were amenorrheic for 45 months. Two of these were followed, one re-established normal periods without treatment in 3 months, and the other in 6 months with estrogen administration.

A comprehensive study of the Theresienstadt concentration camp was made by Bass[1] who compared two groups as to rates. Group A consisted of 3,000 women, housed 70 to 80 to a barracks, sleeping in three-tiered beds, and experiencing every threat of extermination that such typical camp situations presented. Group B consisted of 120 women who were employees living with their families in small private rooms, but on the same diet as Group A. Group B, however, were a maintenance administrative group unthreatened by extermination. The frequency rate was 54 per cent in Group A and 25 per cent in Group B.

Among this large combined group, 60 per cent of the women with amenorrhea had stopped menstruating immediately after internment, that is, before their nutritional status had been seriously altered; 25 per cent developed amenorrhea after one month, 2.5 per cent after 3 months, and 2.5 per cent every month thereafter. Ninety-four per cent recovered spontaneously in 18 months, and the mean recovery period was 10 months. Those remaining amenorrheic for more than 18 months were considered to have "definitive amenorrhea." Most resumed their cycles in the 6 to 12 month period after their release and at a time when malnutritional effects were still pronounced. Consequently, Bass concluded "that the cause of camp amenorrhea was not a physical lesion provoked by long internment; malnutrition, hypoproteinemia, or avitaminosis played no role." Among the 5 per cent in whom amenorrhea persisted more than one and one-half years, 47 per cent developed a menopasual syndrome with uterine involution.

Bass was unable to correlate the amenorrhea with height, weight, coloring, body build, gynecologic data, or previous fertility. He believed, however, that age was a factor since the young women were more susceptible while those more than 40 were more resistant to the development of the symptom.

Two Dutch women physicians[11] who were interned in Indonesia in the camp at Tangerang studied the internees of the camp (1944-1945). This camp was the final one to which most of the prisoners were sent, that is, they had been transferred from several previous "wijk" areas or prisons in all cases, and stayed there during the final year of the war. A "wijk" was a policed group in an area within a city, run as a camp, overcrowded and underfed, but victims were not isolated as in prison, nor in barracks as at Tangerang. It could best be compared to a policed ghetto.

The authors divided the patients into four groups according to the duration

and site of their previous internment. Group I, of upper middle class Dutch origin, were first confined in a ghettolike area in Soerabaja and then transferred to Tangerang. It included many ill with dysentery, malaria, etc. Three per cent became amenorrheic while in Soerabaja, a further 71 per cent in Tangerang. Of those who became amenorrheic in Tangerang, 79 per cent did so after one or no periods, namely, immediately.

Group II came from a prison in Soerabaja, had been interned longer, and were of European or Iraqian Jewish origin. Twenty-four per cent stopped menstruating abruptly in Soerabaja, a further 28 per cent in Tangerang.

Group III came from a ghettolike enclosure in Batavia, which was far worse than that in Soerabaja, where the food was in shorter supply, and the terror and fear of death maximal. They were, however, living with other female members of their families and had slightly more privacy. Nineteen per cent became amenorrheic in Batavia, a further 44 per cent in Tangerang.

Group IV were from prisons in Batavia and consisted of Jewish women of English, French, Belgian, and Dutch origin. All but the Dutch were imprisoned in 1942, the Dutch in 1943. Fifty per cent became amenorrheic in Batavia, an additional 43 per cent in Tangerang.

Analysis of the data made a number of points quite evident. The less the previous stress of confinement, the higher were the rates of amenorrhea after admission to Tangerang (see Group I). Irrespective of whether the amenorrhea began with first imprisonment or in Tangerang, 59 per cent ceased menstruating abruptly, that is, they had one or no periods. The pre-Tangerang rates of the two prison groups were higher than in the ghetto groups (24 per cent and 50 per cent as compared with 3 per cent and 19 per cent). Only 8 per cent of the women who became amenorrheic in Tangerang subsequently resumed their menstrual periods while still interned. Although the authors had no opportunity to follow up the internees, they subsequently learned from colleagues that nearly all resumed menstruating shortly after liberation. The young woman to whom we referred previously used the words "immediately—long before we had gained weight."

An extraordinary report by Stieve,[38] an eminent endocrine histologist,[13,40] written in 1940 revealed that prisoners indicted for severe crimes and later executed, showed extensive ovarian and testicular atrophy at autopsy. Without exception the women between the ages of 20 and 29 were amenorrheic although prior to that time they had normal periods. Histologic examination revealed an absence of corpora lutea, the presence of many primary follicles but no secondary ones, and an increase in the number of atretic follicles. The endometrium consisted of a single stratum without cilia and few glands. The Fallopian tubes were free of ciliated cells, there were protoplasmic and nuclear changes indicating early disintegration. What is not mentioned is the number of autopsies, the crimes, the prison, or the nutritional status of its inmates. Only the extent of time between imprisonment and death (62 to 154 days) was reported. It is pertinent to add, however, that the site of detention was a "prison," not a "camp." Irrespective of other circumstances this is certainly a very short indictment-execution period and was associated with gonadal disintegration which was even more precipitous and severe than in starvation.

Prognosis has been discussed along with frequency in some of the references cited. Apparently, the prognosis is generally excellent but difficulties in following the cases after liberation makes accurate rates impossible. Horvath and colleagues[14] claimed that 32 per cent of the amenorrheic patients menstruated immediately after liberation or within 4 months without treatment. Most of the remainder of subjects menstruated within 8 to 16 months in spite of residual weight loss, breast atrophy, hypotonicity, decreased body temperature, etc. He postulated that hormonal treatment was entirely ineffective and expressed his belief that "only 12 to 20 per cent were irreversible," a figure considerably higher than that of other investigators.

PHYSIOLOGIC CONSIDERATIONS

In a peacetime study, Hauser and co-workers[12] consider the amenorrhea of 67 per cent of 138 cases under 40 years of age as being "functional," such as, an amenorrhea not due to myomas, cystic ovaries, congenital defects, etc.

A good deal of controversy exists as to the mechanism responsible for the development of amenorrhea. Thus, it is uncertain whether the endocrine pathway is primarily pituitary to ovary or directly and solely ovarian. Most of this work is based on gonadotropin assays, with or without estrogen assays. Klinefelter[20] and Reifenstein[33] studied a group of patients with "psychogenic" amenorrhea. They found normal follicle-stimulating hormone (FSH) excretion with low estrogen excretion, and postulated that an inhibition of hypothalamic impulses to the pituitary gland are responsible and consequently a lack of luteotropic hormone (LH) ensues. They offer no explanation as to why the estrogen lack does not increase the FSH output as occurs in the classic menopausal syndrome. The concept of a "hypothalamic amenorrhea" has been generally accepted, even though no data on the excretion of LH exist in support of the hypothesis. Fletcher and Brown,[7] using a more recently developed technique, found that while the rate of gonadotropin excretion in 18 cases of amenorrhea was variable, there were only 5 women with a "relatively low" interstitial-cell-stimulating hormone (ICSH) excretion. "In no patient was there good evidence of a low excretion of FSH relative to ICSH."

On the basis of his studies of a small number of patients, Brown[4] stated that the "absence of qualitative fluctuation of the gonadotropin contrasts with the findings during the menstrual cycle. This supports the suggestion that in secondary amenorrhea there may be a derangement in the rhythm of gonadotropin secretion." In accord are the observations by Whiteacre and Barrera[42] on 2 women who showed a low excretion of estrogen and a questionable increased excretion of gonadotropin. While Decourt and Michard[5] found normal rates of gonadotropin excretion, Limage and Boute[22] made an heroic attempt to differentiate types of amenorrhea by the assay findings. Among 19 women, 5 had increased urinary gonadotropin with low estrogenic activity (smears) and their conditions were designated as "ménopause précoce," while 8 had normal FSH with some estrogen effect and their conditions were designated as "hypothalamic amenorrhea." Two cases of low FSH were considered of psychic origin although the patients' histories indicated no more conflict or trauma than those in the

"menopausal" group (2 with marriage or family conflicts, one postbombardment, one postoperative [endometrial in origin?]), or the "hypothalamic" group (4 with manifest psychological conflicts, one anorexia nervosa). The remaining 4 patients had normal FSH with varying medical or gynecologic causes for their amenorrhea. Netter and associates[30] followed the same type of reasoning in their paper entitled "Aménorrhées Ovarioplégiques" and cited 10 women with amenorrhea of from 2 to 14 years, all with flushes, all with increased gonadotropin excretion, all with some severe emotional shock preceding the amonorrhea.

Goldzieher and Goldzieher[9] postulated that the defect in psychogenic amenorrhea is not a decreased output of estrogens, but rather an increased destruction by the tissues as demonstrated by "extraordinarily rapid destruction of administered steroid (Premarin)."

Into this chaos one small but pertinent fact appears. Loeser[23] did endometrial biopsies on 4 amenorrheic women (3 in whom the onset followed bombings, one with a fear of pregnancy), and documented the findings in Table II (the biopsies were interpreted by Novak who had no knowledge of the patients' histories). These findings are consistent with the concept that, irrespective of what may be occurring in the hypothalamus-pituitary-ovary-endometrium chain, the process occurs promptly and remains for at least one cycle, for example, about 4 weeks, in "status quo" so far as the endometrium is concerned.

In the absence of studies employing accurate methods for assaying the FSH and LH in the urine, it appears fruitless to theorize about the activity of the pituitary of patients with amenorrhea. Undoubtedly data will be provided in the future which will reveal some derangement in one or another locus of the established pathways from higher centers to hypothalamus, hypothalamus to pituitary, hypothalamus to ovary via autonomic nervous system, and autonomic nervous system directly to endometrium. A variety of neurophysiologic studies make it evident that the type of psychogenic amenorrhea discussed herein is initiated in the cerebral cortex, travels one or all of these routes to one or all of the possible target organs, and that with continuing psychic stress this effect may or may not be added to by hormonal stimuli and responses. Although there may be an aberration in the secretion of gonadotropin by the pituitary gland or a decrease in the secretion of the ovarian hormones, the refractoriness of the amenorrhea to hormones[1,8,11,14,22,23,27,39,41-43] and the spontaneous cure which occurs with relief from stress and reassurance, or with psychotherapeutic techniques[21,22,37] suggest that neurogenic influences continue throughout the period of amenorrhea. The relatively few women who remained amenorrheic after their liberation from prison, etc., probably developed some irreversible ovarian and/or uterine atrophy.[38] In such instances (as in the series of Netter and his group[30]), the levels of gonadotropin may have increased either in an effort to stimulate the atrophied ovary or because of decreased utilization, with the resultant classical menopausal syndrome.

Insofar as much of the aforementioned data are reminiscent of anorexia nervosa, it is noteworthy that, as with amenorrhea, the pathogenesis of this disease is also unknown and its relationship to schizophrenia not established. Nevertheless, it is fairly clear that anorexia nervosa is a psychiatric derangement

TABLE II*

AGE	PROBABLE PRECIPITATING FACTOR	DAY OF CYCLE ON WHICH SHOCK OCCURRED	ESTIMATED DAY OF CYCLE BY ENDOMETRIAL BIOPSY (DAYS)	TIME OF BIOPSY AFTER L.M.P. (DAYS)
30	Bomb	10 (usually 32 day cycle)	6–7	38
39	Bomb	13	12	41
28	Bomb	18	16–18	39
42	Intercourse without contraceptive	15	16–18	38

*From Loeser.[23]

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which is associated with a depression of pituitary, ovarian, adrenal, and thyroid function, as well as with a marked loss of weight. As has been emphasized by others,[17,29] the amenorrhea of anorexia nervosa may precede the weight loss. Also, as with uncomplicated amenorrhea, there is a good deal of confusion as to the actual status of gonadotropin secretion in patients with anorexia nervosa.[2,3,6,15,20,24,32,34] It is quite possible that some overlap may exist in marginal cases of both groups and that they may have a related psychophysiologic etiology.

PSYCHOLOGICAL CONSIDERATIONS

A great deal has been written about the psychological determinants of secondary amenorrhea. Unlike the endocrine relationships, the role of psychological factors are apparently quite well agreed upon and have been excellently summarized in the review by Kelley and his associates.[18] The latter have analyzed the psychological test data on 26 patients with amenorrhea as well as that of a control group and concluded that ". . . correlative psychic unbalance was observed in the form of extreme degrees of psychosexual immaturity, oral conflict and schizoid thinking." The conclusion was reached that the amenorrhea in some instances constitutes a symptom of neurohumoral disorder of function, the psychic correlates of which are the psychopathologic manifestations described above. It must be emphasized, however, that the patients who were studied had been sent to the authors because of psychiatric problems whose presenting somatic manifestation was amenorrhea. Menzer-Benaron[28] extended this conclusion with a detailed report of a patient in psychoanalytic treatment.

In contrast, Decourt and Michard[5] stated that, "With certain exceptions, psychogenic amenorrhea is not accompanied by neurotic changes. The patients present no characteristics of a psychiatric disorder and are not sent to a psychiatrist—but rather to an internist, gynecologist, or endocrinologist."

DISCUSSION

When the diverse data reviewed herein are regarded as a unit rather than a conglomeration of isolated facts, it becomes evident that psychogenic stimuli lead to amenorrhea in direct proportion to the stress. The special characteristics of

such stress seem to be factors which induce separation and/or hopelessness, whether in the college freshman, the camp internee, or the prisoner.

This is in no way to deny that the underlying psychophysiologic processes may have to do with sexual denial, immaturity, etc. In the neurotic and psychotic patients referred to previously, it might be possible to demonstrate that the amenorrhea is initiated as a phantasied "separation" utilized for psychopathologic purposes. We must reiterate here, however, that the psychiatrists are seeing the isolated instances of women who are psychologically "sick"; they are not screening all those who have amenorrhea in any population group meeting epidemiologic criteria. Thus, it seems important to emphasize that if a symptom can under certain circumstances have a prevalence rate of 100 per cent, the word "neurosis" is probably inappropriate as an explanation. Perhaps we should invoke the simpler folklore explanation that gonadal function is a physiologic luxury available only when self-preservation is not in question.

The present state of our knowledge does not permit us to go any further than postulating the separation-hopelessness hypothesis. In the groups that comprised the Dutch East Indies prisoners, the nuns were the only group that did *not* become amenorrheic.[19] One may wonder whether the lack of susceptibility to amenorrhea could be attributed to the probability that in such a dedicated group of women "separation" or "hopelessness" was not possible; they were secure in the vows of their religion from either threat.

SUMMARY

The frequency rates of secondary amenorrhea when examined epidemiologically appear to be quantitatively related to separation from home and family and to the extent of the threat associated with such separation. In peacetime circumstances the rates are low but increase to 100 per cent in those about to be executed.

Such amenorrhea definitely antedates the malnutrition which is associated with many of the situations where high rates occurred. In the large majority of instances, amenorrhea developed immediately after the separation. The prognosis is excellent if the stress can be adapted to or removed. However, when the amenorrhea is preceded by evidence of psychosexual immaturity, neurotic or psychotic, the prognosis is more dubious.

There is some evidence that age of menarche and age at separation influence the rates.

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Pathobiology

ABNORMAL TRACE METALS IN MAN: LEAD

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INTRODUCTION

LEAD has been considered toxic to man for many years. Although its acute toxicity is relatively low, it accumulates slowly in tissues when exposure exceeds elimination, finally provoking the characteristic overt syndrome of chronic plumbism. Little is known, however, of its recondite biologic activity in small concentrations or after a lifetime of exposure to amounts "normally" found in food, water, or air, although a vast amount of experimental work has been done on larger exposures for the past 70 years.

The body of the "standard American man" contains approximately 80 mg. of lead, much of which is in bone, but with concentrations of more than 1 mg./kg. (wet weight) in the aorta, kidney, liver, and upper respiratory tract.[1,2] Lead was found in every human liver and in all but a rare kidney and lung from human bodies analyzed from the Orient, India, Middle East, Europe, Africa, and the United States.[3] It was present in all newborn infants and children.[4] Of American human tissues it was found in all specimens of aorta and pancreas, and in almost all prostates, spleens, and testes examined.[1,4] Therefore, exposure to lead appears largely world wide, although geographic variations in concentrations may exist.

It is the purpose of this report to answer, in so far as possible, three questions: (1) What are the sources of the lead found in human beings? Many surveys of food and water have been made,[5,6] but it appeared rewarding to reexamine the matter in order to ascertain whether or not exposures have changed in the past 20 years. (2) Is lead by any possibility an "essential" or necessary trace element for living organisms? To our knowledge, no one has proposed that this might be the case, although lead is more prevalent on this planet than are some essential trace metals, such as cobalt or molybdenum. (3) Is lead primarily

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an industrial contaminant, a product of a civilization based on metal, or is it mainly of natural occurrence? While man has been exposed to industrial lead from the beginning of history, are wild animals also exposed? A most important question regarding esoteric toxicity in small doses cannot be answered until lifetime studies of small mammals have been completed. Partial answers to these questions were obtained.

METHOD

Samples were ashed in a muffle furnace at 450°C. for 24 to 48 hours after drying to constant weight. Samples of 1 L. of water were evaporated to 5 to 6 ml., treated with 1 ml. HNO_3 and 1 ml. $HClO_4$, evaporated to dryness, and fumed to drive off the acids. The residues were taken up in deionized water with a resistance of one million ohms or more. Lead was determined by the microanalytic method of Sandell for biomaterial, which depends upon dithizone extraction.[7] Optical density was read at 520 mμ in a Bausch and Lomb Spectronic 20 colorimeter. Recoveries of known amounts of lead added to unknowns usually were 100 per cent. Limits of sensitivity were approximately 0.05 μg per sample. Small amounts of lead in reagents appeared in the blanks and were subtracted from the analytic results.

ORGAN ACCUMULATIONS OF LEAD IN MAN

In Table I are shown the mean concentrations of lead found in kidney and liver in various areas of the world,* by spectrographic analyses of tissues.[3] Levels in Africans were generally lower than in other races, especially in nonurban natives. Figs. 1-3 indicate the mean concentrations of lead in aorta, kidney, liver, lung, pancreas, and bone at different ages in American human beings. There appears to be an accumulation for five or six decades. Noteworthy are the presence of lead in the newborn, indicating placental transfer, and the low values in the bones of infants and children. Data in curves were analyzed for coefficients of correlation (r) and correlation ratios (Eta)[8]; significances are shown in the legends. The curves for liver and pancreas were not statistically valid either as curves or straight line functions.

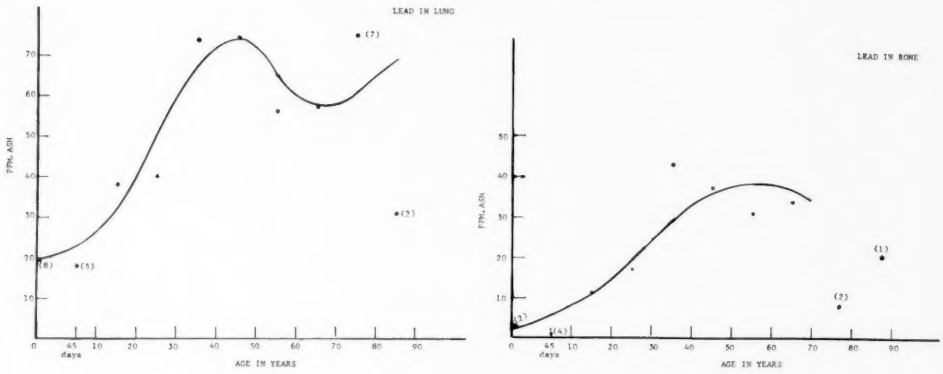
LEAD IN COMMON FOODS

Table II shows the lead concentrations by microanalytic chemical methods in a variety of foods. A few were devoid of lead and an additional few had small amounts. On the other hand, not many had high contents, most showing less than 0.5 ppm. These data are in general comparable to or lower than those obtained by Kehoe, Cholak, and Story 20 years ago.[5] An attempt to calculate the amount of lead per 100 calories of each food is also shown in the table.

LEAD IN WATER

A preliminary survey of potable waters in this area revealed little or no

*Tissues from the United States were collected by Dr. I. H. Tipton and Miss M. J. Cook; those from Africa by Dr. H. M. Perry, Jr., and those from other areas of the world by one of us (H. A. S.).



A. *B.*

Fig. 1.—Change in concentration of lead (ppm. ash) with age in *A*, lung (167 cases) and *B*, bone (79 cases), mean United States values.[1,3] Numbers in parentheses refer to numbers of cases in that decade, when less than 9. Bone ash varied from about 20 to 30 per cent of wet weight; lung ash 0.9 to 1.7 per cent. Statistical analyses[8] for the curve of the concentration in the lung showed: E = 0.28, S.E.$_E$ = 0.07, not significant; r = 0.21, p $<$ 0.01. For that of bone: E = 0.58, S.E.$_E$ = 0.75, p $<$ 0.05; r = 0.32, p $<$ 0.01.

detectable lead, except in instances where lead piping was used. In view of the constant supervision of public health agencies on the lead content of potable water, this survey was not further developed. To determine solution of lead by soft water in a new piping system, analyses were made from a spring and a newly installed tap at the end of 200 feet of black polyethylene and copper pipes, the latter joined with lead solder. The results are shown in Table III. The total hardness of the water was 18 ppm. and the pH, 6.0.

To ascertain the presence of airborne lead, snow was collected from town areas and from a mountain more than a mile from a road. The elevation of the town was approximately 100 M., of the mountain 550 M. above sea level. The results are indicated in Table IV. Presumably the lead came from the combustion of petroleum products at or near ground level, as is inferred from the table.

LEAD IN ANIMAL TISSUES

In order to ascertain whether or not exposure to lead occurs in animals other than man, the livers, kidneys, and a few other tissues from both wild and domestic animals were analyzed. The results are shown in Table V. It would appear from these examples that exposure to lead is not confined to man.*

SOURCES OF LEAD IN ANIMALS

Table VI shows the results of analyses of vegetation, including some samples of food for animals and birds. The high concentrations in apple trees are noteworthy. Although spraying with lead arsenate was begun in 1894, it is doubtful that these trees were ever so sprayed, for they were seeded at some distance

*Tipton found 3.6, 0.16, and 0.27 ppm. lead in the kidneys of three female Tennessee deer and none in a male.[3]

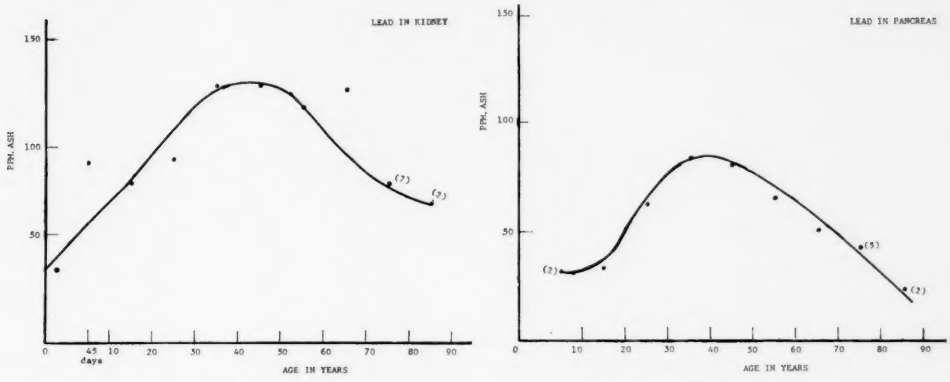


Fig. 2.—Change in concentration of lead (ppm. ash) with age in *A*, kidney (194 cases) and *B*, pancreas (143 cases), mean United States values.[1,3] Numbers in parentheses refer to numbers of cases in that decade when less than 9. Kidney ash varied from 0.8 to 1.3 per cent of wet weight, pancreas ash 0.7 to 1.6 per cent. Statistical analyses[8] for the curve of the concentration in the kidney showed: E = 0.61, S.E.$_E$ 0.045, $p < 0.01$. For that of the pancreas: E = 0.136, S.E.$_E$ = 0.082, not significant; r = 0.02, not significant.

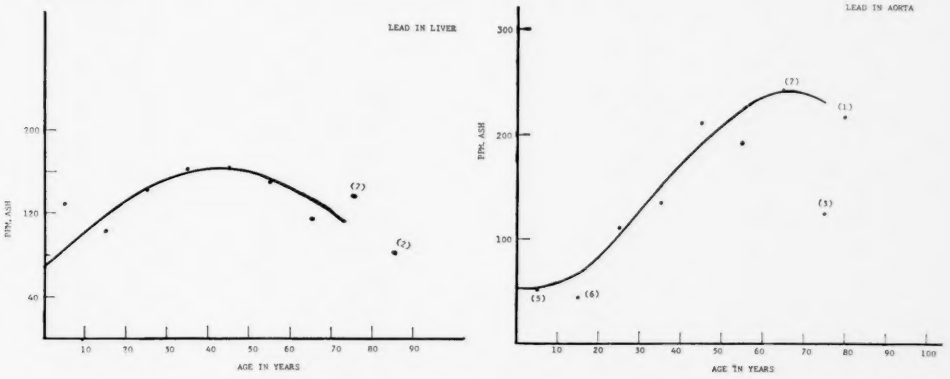


Fig. 3.—Change in concentration of lead (ppm. ash) with age in *A*, liver (207 cases) and *B*, aorta (102 cases), mean United States values.[1,3] Numbers in parentheses refer to numbers of cases in that decade when less than 9. Liver ash varied from 0.8 to 1.8 per cent of wet weight, aortic ash from 0.5 to 3.4 per cent. Statistical analyses[8] for the curve of the concentration in the liver showed: E = 0.22, S.E.$_E$ = 0.066, not significant; for that of the aorta E = 0.396, S.E.$_E$ = 0.084, $p < 0.05$.

from orchards over 100 years old which has now virtually disappeared except for dead or dying old trees in the midst of a forest of marketable hardwood. In Table VII are the concentrations of lead found in a variety of building and other materials to which laboratory animals might be exposed. The impossibility of obtaining a strictly lead-free environment is clear from these results, although low levels in food are possible to achieve by careful choices.

DISCUSSION

The present report is the second of a series on the presence and sources of "abnormal" trace elements in man (and animals). It attempts to obtain data which will lead to a decision as to whether or not certain metals are essential,

TABLE I. LEAD IN ADULT HUMAN KIDNEY AND LIVER FROM VARIOUS AREAS OF THE WORLD. MEAN VALUES, PPM. ASH. (From Tipton, et al.[1,3,4])

AREA	NUMBER OF SAMPLES	KIDNEY PPM.	LIVER PPM.
United States Mainland—A*	88	120	150
—B†	18	92	120
Honolulu	5	84	150
Alaska	2	57	37
Cairo	3	110	200
Beirut	6	76	125
Bombay	9	88	74
Delhi	10	41	55
Vellore	13	98	92
Bangkok	9	91**	74**
Manila	4	51	77
Hong Kong	10	100	213
Taiwan	9	160	125
Tokyo	10	98	94
Kyoto	11	37**	105
Nigeria	19	37‡	94
Lambarene	6	57	104
Welkom	5	38**	60
Uganda	4	28	25
Usumbura	11	23‡	20**
Bern	9	50	100
Total and range	261	23–160	20–213

The median per cent of ash in kidneys was 1.1 (90% range 0.8-1.3) and in livers 1.3 (90% range 1.0-1.8).

No geographic variations in concentrations of lead in the liver or kidney from data from 7 cities of the United States were found, maximum deviations from the mean being 30 per cent for kidney and 25 per cent for liver.

*U. S.—A = Accidental deaths.

†U. S.—B = Cardiovascular deaths.

**Trace In one, not used in mean.

‡None detectable in one, not used in mean.

or are industrial or natural contaminants, and whether or not they accumulate in man. The first report dealt with cadmium.[9] We are interested in the 29 common trace elements found in man in easily detectable amounts.[1] Of these, lead ranks twenty-third in order of magnitude of abundance in the universe.[10] It ranks sixteenth in the earth's crust and ninth in sea water, from which all life evolved. In alfalfa (lucerne) it ranks eighteenth of 20,[11] and in coal, eighth of 14.[10] In the body of man it ranks seventh (omitting all bulk elements), being exceeded only by essential iron, zinc, and copper, and by rubidium, strontium, and aluminum.[2] Its concentration considerably exceeds those of manganese, molybdenum, and cobalt in the whole body and in such tissues as the liver, spleen, kidney, lung, and muscle.[2]

For a working hypothesis, one can suspect a trace metal to be essential for mammals if it has the following characteristics: (1) It is ubiquitous on the earth's crust and therefore readily available. (2) It is present in plants and in at least one mammalian organ or tissue. (3) It shows biologic activity in vitro, affecting one or more common enzyme systems. (4) Its molecular weight is (probably) below elements in the lanthanum series. (5) It is relatively nontoxic to mammals orally, a dose equal to the total body pool being readily tolerated. Lead satisfies only the first two of these criteria.

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TABLE II. LEAD IN FOOD

SAMPLE	μG/GM WET WEIGHT	μG/100 CALORIES*
Condiments		
Table salt, iodized	0.0	——
Pepper, black	0.40	——
Sugar, white, granulated	0.0	——
Sugar, white, granulated	0.07	1.8
Molasses, New Orleans	0.53	20.4
Baking powder	1.50	——
Yeast, dry	1.17	——
Sea Food		
Shrimp, frozen, uncooked	0.31	27.2
Shrimp, fresh	0.45	39.4
Lobster, claw meat, Maine	2.50	111.0
Crabmeat, canned, Japan	0.06	4.8
Clams, fresh frozen	0.15	31.3
Oysters, canned, American	0.13	26.0
Scallops, fresh	0.15	15.0
Anchovies, fillets	0.87	29.9
Kippered herring, Norway	0.30	15.0
Sardines, canned, Portugal	0.75	25.0
Swordfish, Atlantic	0.17	17.0
Haddock, Atlantic	0.27	27.0
Mean	0.49	——
Meats		
Beef, chuck	0.20	11.3
Beef, marrow	0.07	——
Lamb, chop	0.15	8.0
Lamb, marrow	0.37	——
Pork, chop	0.16	5.3
Gelatin, dry	0.57	14.3
Egg, whole	0.0	——
Egg, whole	0.15	9.0
Mean	0.21	——
Grains and Grain Products		
Wheat, winter, seed treated	0.19	5.6
Wheat, crushed, Vermont	1.39	40.8
Wheat, Japanese #4	0.0	——
Wheat, Japanese #6	0.24	7.1
Flour, wheat, all-purpose	0.23	7.0
Flour, wheat, all-purpose	0.52	14.9
Flour, wheat, Japanese #5	0.52	15.3
Bread, stone ground, whole wheat	0.86	34.4
Wheaties	0.10	2.5
Puffed Rice	7.49	214.0
All-Bran cereal	0.21	7.0
Grapenuts	0.10	2.8
Oats, seed	0.62	15.5
Oats, feed	0.60	15.0
Oats, quick cooking	0.56	14.0
Rye, seed	0.20	6.0
Buckwheat, seed selected	0.19	5.4
Rice, American, polished	0.06	1.2
Rice, Japanese, #2 polished	0.07	1.5
Rice, Japanese, #5 unpolished	0.0	——
Rice, Japanese, 204 samples	0.10	2.8

*From McCance, R. A., and Widdowson, E. M.[27]

TABLE II—CONT'D

SAMPLE	μG/GM WET WEIGHT	μG/100 CALORIES*
Grains (Cont'd)		
Corn, frozen	0.58	16.5
Corn meal, New Hampshire	0	——
Corn, 50-year old, on cob	0.16	4.5
Corn oil	0.0	——
Vegetable shortening	0.27	3.4
Mean	0.37	——
Vegetables		
Potatoes, white, raw	0.12	13.8
Cabbage, white	0.0	——
Cabbage, red	0.02	10.0
Kale, organically grown	1.26	504.0
Lettuce, garden, organically grown	1.04	36.6
Lettuce, commercial	0.03	27.2
Kohlrabi, leaves, organically grown	0.28	112.0
Broccoli, frozen	0.07	49.0
Beet greens	0.36	144.0
Swiss chard, organically grown	0.75	300.0
Spinach	0.16	64.0
Cauliflower leaves, organically grown	0.09	82.0
Celery, green	0.10	100.0
Chicory, fresh	0.81	810.0
Escarole, fresh	0.27	270.0
Beans, string, frozen	0.01	1.1
Beans, string, canned	0.03	3.3
Beans, red kidney, dried	0.16	5.3
Beans, yellow eye, dried	0.21	7.0
Beans, navy, dried	0.0	——
Peas, frozen, fresh	0.02	3.0
Peas, split, dried	0.0	——
Peas, canned	0.11	12.7
Tomato juice, canned	0.08	53.3
Tomato, fresh	0.02	13.3
Apple, raw, McIntosh	0.38	76.0
Pear, raw	0.03	7.5
Mean	0.21	——
Fluids		
Milk, whole, fresh local	0.0	——
Milk, skim, dried, packaged	0.79	24.2
Milk, skim, dried, bulk, same	0.02	0.6
Milk, evaporated, #1	0.05	3.2
Milk, evaporated, #2	0.04	2.6
Cola, #1	65/L.	13.0
Cola, #2	18/L.	3.6
Mineral water, bottled, Hot Springs, Ark.	5/L.	——
Ginger ale	10/L.	——
Tea, Orange Pekoe	1.37	——
Cocoa, dry	0.10	2.0
Cider, apple, local	90/L.	18.0
Vinegar, cider, local	100/L.	——
Beer, canned	40/L.	8.0
Wine, red	50/L.	——
Cigarettes		
Filtered, whole	24.11	482.0/pack

*From McCance, R. A., and Widdowson, E. M.[27]

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TABLE II—CONT'D

SAMPLE	μG/GM WET WEIGHT	μG/100 CALORIES*
Spices		
Cinnamon	0.11	
Nutmeg	0.41	
Cloves	0.10	
Allspice	0.64	
Chili powder	0.18	
Bay leaves	0.55	
Animal Foods		
Dog food	0.0	———
Beet pulp	1.80	360.0
Calf food, prepared	0.32	32.0
Bird seed, wild	0.65	———
Wheat, poultry	0.02	0.6
Rye, seed, dried milk and corn oil diet #1	0.37	9.3
#2 (bulk milk)	0.20	5.0
#3	0.20	5.0
#4	0.20	5.0
#6	0.26	6.5
#9	0.20	5.0
Poultry wheat, dried milk and corn oil diet	0.08	2.0
Dog meal, A, 1954	94.0	Spectrographic Method†
1958	1.9	Chemical Method†
Dog chow, B, 1954	14.8	Chemical Method†
1958	0.40	Chemical Method†
Rabbit chow, 1954	trace	Chemical Method†
1958	1.7	Chemical Method†
Rat diet 1958	1.9	Chemical Method†
Wheat and milk diet, 1958	0.7	Chemical Method†

*From McCance, R. A., and Widdowson, E. M.[27]

†These analyses were done in 1954 and 1958 by Robert E. Keenan, Principal Spectrochemist, United States Public Health Service, Occupational Health Field Headquarters, Cincinnati.

TABLE III. LEAD IN POTABLE WATER (μG/L.)

SOURCE	Pb	PIPING AND REMARKS
Tap, laboratory, cold	2.3	Brass, town water supply
hot	4.5	Brass
Spring, forest, piped #1	0	600 feet galvanized, copper in house
Spring, forest, unpiped #2	0	
Spring, field, piped #1	4.2	Lead, 75 years old
Spring, field, piped #2	112.5	Lead, 50 years old
Well, artesian, piped	0	Galvanized
Spring, forest, old, at source	0	Rock walls
after rebuilding	0	Poured cement walls
through pipes, turbid	24.0	First run through 210 feet black polyethylene, 10 feet copper and hot water heater "glass-lined"
filtered	10.0	
six weeks later	3.3	
Mineral water, bottled	5.0	From Hot Springs, Ark.

TABLE IV. LEAD, CADMIUM, AND NICKEL IN MELTED SNOW (μG/L.)

SAMPLE LOCATION	AGE (DAYS)	Pb	Cd	Ni
A—Edge of town 100 M. elevation				
1. Open porch 10 M. high	0	0	0	0
2. 300 M. from street, open lawn	0	5.25	0.38	0
3. 3 M. from street, lawn	0	12.0	0.5	0
4. Side of street, plowed and fresh	0+	77.0	0.75	0
B—Top of mountain, 550 M. elevation				
1. Open lawn 20 M. from house, fresh	0	0	0	0
2. Same, old	8	3.9	0	0
3. Forest, 100 M. from house	2	1.0	0.5	0
4. Near auto exhaust 5 minutes	0	1858	0.98	0.56

Note: Location "*A*" was on the grounds of the Brattleboro Retreat, bordering a fairly well-traveled road. The area is suburban, verging on rural. Sample A-1 was from one of the buildings, which lies approximately halfway between location of samples A-2 and A-3 and 4. Oil is used for heat.

Location "*B*" was near an old farmhouse close to the top of a mountain at the road's end, one mile from a country road and nearest other house. It lies approximately four miles from the nearest highway and is 400 M. higher. Oil is used for heat. Auto engines run approximately 5 minutes per day. Sample B-2 and B-3 were exposed only to chimney smoke from wood and oil.

TABLE V. LEAD IN ANIMAL TISSUES

SAMPLE	μG/GM WET WEIGHT	REMARKS
Liver		
Salmon, young, Miramachi R.	0.88	First return to river
Salmon, 4 years+, same	0.71	4 trips to river
Starling	2.12	Shot, 22 cal. bullet in neck
Robin	1.10	Killed accident
Ruffed grouse	0.56	Found dead
Red squirrel, female	1.37	Trapped
Red squirrel, male	2.08	Trapped
Rat, Long-Evans, 33 days old	0.39	
Same 28 days old	0.83	
Same 145 days old	0.0	"Lead-free" diet
Rabbit, wild	0.57	Trapped
Deer, #2	0.0	Shot
Deer, #3	0.36	Shot
Deer, #4	0.50	Shot
Deer, #5	0.45	Shot
Pork, #1	0.82	
Pork, #4	0.26	
Beef	0.67	"Organically" raised
Rat, Long-Evans weanling, 28 days	0.37	Rockland Farms
Rat, Long-Evans weanling, 31 days	0.83	Rockland Farms
Human (mean)	2.0	Ref. 2
Kidney		
Ruffed grouse	26.17	Found dead
Gray squirrel, male	1.47	Shot
Rabbit, wild	2.91	Trapped
Deer, #1	0.57	Shot
Deer, #2	0.72	Shot
Deer, #3	0.45	Shot
Deer, #4	0.40	Shot
Deer, #5	1.40	Shot

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TABLE V—CONT'D

SAMPLE	μG/GM WET WEIGHT	REMARKS
Kidney (Cont'd)		
Deer, #6	0.34	Shot
Deer, #7	1.17	Shot
Deer, #8-a	0.20	Shot
Deer, #8-b	0.0	Shot
Pork, #1	0.98	
Pork, #3	0.84	
Pork, #4	0.26	
Beef	0.51	"Organically" raised
Human (mean)	1.24	Ref. 2
Bone		
Beef, foreleg	0.16	
Human (mean)	6.6	Ref. 2
Muscle		
Beef	0.20	
Pork	0.16	
Lamb	0.15	
Human (mean)	0.14–0.19	Ref. 2
Heart		
Chicken	1.71	
Gray squirrel	0.50	
Human (mean)	<0.2	Ref. 2
Aorta		
Human (mean)	2.51	Ref. 2
Male, aged 82	2.13	

Essentiality of Lead.—From its ubiquity in almost all natural material and in wild animals, and from its concentration in the biosphere, one might infer that lead is an essential trace element. The prevalent belief in the toxicity of lead, however, has argued against such an hypothesis, although another metal equally or more toxic (cadmium) has been considered as possibly essential.[12]

Lead, like cadmium, when it acts at all upon an enzyme system or a living organism, is inhibitory,* mainly, perhaps, by binding free sulfhydryl groups.[13] On living organisms, lead (chloride) immobilized *Daphnia magna* at concentrations of 0.01 to 1.0 ppm. and was lethal to various fish at 0.1 to 50 ppm., which is in the range of toxicity of zinc and nickel; these three metals were considerably less toxic than copper, cadmium, mercury, and silver ions.[14] It is not as toxic orally for mammals as cadmium and mercury, but is more so than copper, manganese, silver, vanadium, zinc, chromium, molybdenum, cobalt, nickel, and

*This statement is not strictly true. Pb^{++}, along with four other trivalent ions, may further activate phosphoglucomutase which requires Mg. or Mn.[28] Lead has been shown to act as a constrictor of the arteries of the dog's hind limb when perfused in low concentrations.[29] No known enzyme, however, has been shown to require lead, although experiments aimed at finding one have been few.

TABLE VI. LEAD IN VEGETATION

SAMPLE	μG/GM WET WEIGHT
Apple, wild, 6″ diameter tree, #1	0.02
Leaves	4.49
Twigs	20.75
Bark	22.00
Apple, 14″ diameter tree, once cultivated, #2	0.11
Leaves	0.0
Twigs	4.78
Apple, wild, 4″ diameter tree, #3	0.09
Leaves	5.5
Hemlock bark, wild	10.1
Twigs	3.0
Needles	3.2
Spruce twigs, wild	1.6
Needles	2.04
Pine twigs, wild	4.2
Needles	1.8
Sumac berries	0.75
Sawdust, pine, local	1.6
Wood chips, northern New Hampshire	1.83
Peat moss, Sphagnum, #1	1.7
Same, #2	1.6
Hay, fertilized field, #1, tractor baled	1.25
Hay, fertilized field, #2, tractor baled	1.7
Hay, unfertilized field, tractor baled	1.1
Elm, center, grown 1865-1870 (Cd, 0)	0.16
Section grown 1900-1910 (Cd, 0)	0.12
Outer section, 1940-1947 (Cd, 0.01 ppm.)	0.33
Late growth, 1956-1959 (Cd, 0.04 ppm.)	0.74
Bark and cambium (Cd, 0.08 ppm.)	3.9

TABLE VII. LEAD IN COMMON MATERIAL

SAMPLE	μG/GM WET WEIGHT
Scotch tape, filament, glass	1.67
Scotch tape, black plastic	196.00±
Salt, rock, crude, road	0.37
Calcium chloride, crude, road	0.0
Sheet rock	0.75
Sheet rock, plastic	0
Tar paper, building	8.1
Whitewash, old	3.2
Cement, old	0.25
Fabulon, plastic	0.25
Krylon, plastic	0.57
Cork, rubber, A. H. T. Black	1.47
Newsprint, blank, unused	2.41
Paper, shredded, excelsior #1	1.35
Paper, shredded, excelsior #2	2.65
Paper towels	9.78
Polyurethane foam	0.55
Cellophane excelsior, white	2.4
Hytron disinfectant	3.75
Polyethylene, copper colored	1.04

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probably arsenic.[14,15] Calves have survived 2 Gm. per day for two to three years, but poisoning in man has been reported from the use of drinking water containing 0.18 to more than 1.0 ppm., or 0.4 to 2.5 mg. daily in addition to lead in food. Of the total bodily content in man (80 mg.) it is probable that 1 or 2 per cent ingested daily would produce poisoning eventually. Acute toxicity is low; the body pools of antimony, arsenic, and cadmium, taken as single doses, are within toxic limits.[14,15] All of the essential trace metals have a wide margin of safety and their total bodily contents can be given orally, limited only by gastrointestinal irritation.[15] No essential metal, insofar as is known, has a molecular weight above 127 (iodine) and most of them are below 97 (molybdenum). Therefore, the available data imply that lead is not an essential trace metal, but this point cannot be proved. If it is, then, like cadmium, its action is inhibitory.

Accumulation With Age.—Accumulation of lead with age in 6 tissues of American human beings appears to follow a fairly consistent pattern, reaching a maximum in the fifth or sixth decade. In 4 tissues the highest mean concentrations were four to ten times those at birth or in childhood; the curves would be much steeper if total amounts per organ were calculated during the growing period. In the liver and pancreas increases in concentration were smaller.

Concentrations in the liver, kidney, and pancreas were in the same general ranges as those reported by Butt and others[16] from Los Angeles, when calculations for different methods of reporting are made. Those for the lung were less, perhaps as a reflection of airborne lead. Total bodily contents based on these data[1,2] are lower, however, than from other calculations.[6] Although individual variations were wide, three of these curves are statistically significant. Accumulation in the aorta, which rises sharply in early decades, was an unexpected finding; the explanation that lead accompanies calcium is not wholly valid in view of the rapid accumulation in young adults who would not be expected to have much aortic calcification. The apparently low values in bone ash, as compared to ash of other tissues, are functions of the high ash content of bone.

According to these spectrographic analyses [1,2] calculations can be made of the approximate amounts of lead in the major tissues and organs of the "standard" man. These turn out about as follows: muscle, 4.8 mg.; skin, 3.3 mg.; skeleton, 46.2 mg.; blood, 1.6 mg.; gastrointestinal tract, 0.6 mg.; liver, 3.4 mg.; lungs, 0.7 mg.; kidneys, 0.4 mg. From these approximations almost half of the total body pool is in tissues other than bone. Some lead was found in all organs examined except brain and heart, where its occurrence was sporadic. Therefore, the idea that bone is the main area of storage must be revised, although it is the tissue of highest concentration (6.6 ppm. wet weight) (Kehoe and coworkers[5] found 18.8 in long bone and 4.7 ppm. in rib).

Lead Balance.—Monier-Williams gives the following figures for an approximate daily lead balance in a normal individual (in England):

	Intake	*Excretion and Storage*	
From food =	0.22 mg.	Feces	0.30 mg.
From water	0.10	Urine	0.05
From inhaled dust	0.08	Stored in Bones	0.05
Totals	0.40 mg.		0.40 mg.

According to Kehoe[17] the average balances should be adjusted somewhat as follows:

Intake		*Output*	
From food	0.31 mg. (0.1–4.0)	In feces	0.32 mg.
From water	0.02	In urine	0.03
From air	0.02		
Totals	0.35 mg.		0.35 mg.

He has calculated that somewhat less than 10 per cent of ingested lead is absorbed and that the output exceeds the amount of food and water by about 20 μg per day, which probably comes from air. He does not believe that lead in normal amounts continues to accumulate in tissues for a lifetime, but that a balance is achieved.

If the total body pool is about 80 mg.,[2] approximately 2 mg. per year or 6 μg per day would be retained for 40 years, neglecting the small level present at birth. It would be difficult to detect 6 μg by usual methods. If 10 per cent of ingested lead, or 35 μg were absorbed per day, the calculated 6 μg would represent retention of approximately one-sixth, with urinary excretion of five-sixths.* These rough approximations fall within the known values for balances on average American adults.

By spectrographic analyses, Perry and Perry[18] found 120 μg per L. of urine (± S. E. 35.5) or 169 μg per day to be the urinary excretion of 24 people in St. Louis. This amount is higher than usually measured. Kehoe and associates found 29 μg per L., or about 10 per cent of the amount ingested.[5]

The lead concentration in foods found in this study by chemical methods and those reported in 1940 by Kehoe and others,[5] on the basis of results obtained by spectrographic methods, are in similar or lower ranges. Many of their raw materials came from Mexico and a few analyses gave much higher values than ours. There appears to be no obvious increase in lead content of common foods during the past 20 years, as estimated by these data. The use of lead glazes on utensils has diminished considerably as a donor to food.[6]

Lead in Food.—According to our data, a normal diet of 2,300 calories with 100 Gm. protein and 250 Gm. carbohydrate will contain about 0.14 mg. of lead plus a variable amount in vegetables and drinks. Analysis of an institutional diet for one day with beverages of approximately 2,040 calories and weighing 2,526 Gm. wet, showed 258 μg of lead, of which 54 was in the 550 calorie breakfast, 69 in the 800 calorie lunch, and 135 in the 690 calorie dinner (which included gelatin). A diet low in lead can be calculated, using meats, dried legumes, eggs, and fresh milk as the proteins (lead ± 9 μg/100 Gm.), certain Japanese wheat and rice as the carbohydrates (no lead), cabbage and lettuce (4 μg/100 Gm.), corn

*Retained "normal" tissue lead is probably quite strongly chelated to protein, most likely to sulfhydryl groups. Perry and Perry[18] found only a 2.2 fold mean increase of urinary lead in eight patients after daily intravenous injections of disodium calcium ethylenediaminetetraacetate for 10 days. Zinc, on the other hand, increased more than tenfold, suggesting that large amounts are relatively loosely bound. This chelating agent did not mobilize tin, silver, nickel, or molybdenum and increased the excretion of cadmium, manganese, and vanadium less than twofold.

oil and butter. Such diets would contain about 15 μg of lead per day. Contrariwise, diets high in lead can be made up of lobster, whole wheat bread, oatmeal, dried milk, frozen corn, kale, and chicory, washed down with apple cider and colas, which would contain more than 1.3 mg. of lead. A reasonably liberal diet, however, appears to have about the same amount as calculated by Kehoe and others,[5] i.e., approximately 0.29 mg. per day or less. Thus, exposure from food may be somewhat sporadic. If these calculations are correct, it becomes obvious that lead from other sources (most likely air) makes up a small proportion of the intake, and that only a minor fraction is stored in the tissues.

Contrary to common belief, little lead may enter some foods from solders on cans, although the amounts vary with the type of food and the tin content of the solder.[19] In one series of experiments, average values of lead in solution after six months' contact in cans sealed with a tin (2.5 per cent), silver (2.5 per cent), and lead (95 per cent) solder were (ppm.): Evaporated milk 0.38, orange juice 0.04, green beans 0.02, corned beef hamburger 0.05.[19]

Because most foods of whatever nature contain lead in quantities of 0.5 ppm. or less, it is obvious that diets containing large amounts of low-calorie vegetables may have much larger quantities of lead than would more concentrated diets. Table II shows that 1,000 calories of American grain products supply an average of about 0.12 mg. of lead, while 500 calories of leafy vegetables might have as much as 1.0 mg. For practical purposes, therefore, the intake depends more upon the nature of the diet rather than on a choice of specific foods.

Lead in Water.—Water in these days of galvanized and copper piping probably contributes little lead to the body pool. Standards for purity of potable water set a limit of 0.1 ppm.,[20] or about 0.2 mg. per day, a relatively large amount. Analyses of water from 51 locations on 16 major rivers of the United States made twice in 1958 and 1959[21] showed detectable lead by the spectrographic method only 7 times: the Arkansas at Coolidge, Kansas (0.1 ppm.), the Columbia, near Clatskamie, Oregon (0.02 ppm.), the Delaware at Philadelphia (0.08 ppm.), the Mississippi at Delta, Louisiana (0.01 ppm.), and at Burlington, Iowa (0.08 ppm.), the Ohio at Cincinnati (0.03 ppm.), and at East Liverpool, Ohio (0.02 ppm.). The few water supplies analyzed in this area showed at most a few micrograms; most of these waters were soft and acid and therefore liable to dissolve lead from pipes and joints.

Lead in Air.—The amount of lead which air can contribute to the human pool was not measured. Presumably a major portion of airborne lead comes from additives to gasoline used for the past 35 years.* That lead (and cadmium) can accumulate in snow from air is shown in Table IV, where low-lying areas near a road rapidly became contaminated while snow from a 30 foot elevation showed none. Thus a portion of the lead absorbed by man probably comes from gasoline or petroleum as an industrial contaminant.

*The estimated domestic consumption of tetraethyl lead in 1960 was 536 million pounds, or about 150 thousand long tons of lead. This represents approximately 15 per cent of the over-all lead consumption in the United States. About three quarters of this lead was exhausted into the air during driving, from 27 to 40 per cent of that amount settling rapidly.[17]

The amount of lead in air depends upon the locality, in one survey varying from an average of 9.5 μg/M.³ in Philadelphia to 0.05 μg in Minneapolis; and 0.1 to 0.9 in nonurban areas. In general it was larger in the largest cities.[17] According to Tabor and Warren,[22] of 754 samples of air, 83 per cent contained less than 1.6 μg/M.³ and 5.4 per cent contained 3.9 to 2.4 μg; lead was detected in all but 10 samples. At a respiratory volume of 15 M.³ per day, the amount inhaled in a few localities could reach 0.06 to 0.3 mg. but would usually be less than 0.02 mg., provided that all the air inhaled was equally contaminated.

Variations in amounts of lead found in various sections of an elm tree 97 years old by ring count suggest increasing exposures during the last 100 years, especially in the past 30, for there is little circulation in the center of large trees. Presumably this increment represents airborne lead.

The concentrations of lead found in one brand of cigarettes were in the range of those previously reported,[23,24] e.g., 19 to 80 ppm. The amount in tobacco smoke found by spectrographic analyses[24] was, however, only about 1.0 to 3.3 μg per cigarette, providing 20 to 66 μg per pack. This lead is believed to come mainly from lead arsenate [24] and offers to smokers an additional source of airborne metal about equal to that from motor exhaust.

Industrial Contamination.—A further suggestive answer to the question on possible contamination with industrial, especially airborne lead, is found in analyses of human tissues from various areas of the world. Concentration in the kidneys, for example, showed the following major geographic differences (ppm. ash, median values): United States 94, Switzerland 45, Africa 36, Middle East 72, and Far East 82. Values for liver concentrations were: United States 130, Switzerland 59, Africa 66, Middle East 86, Far East 110. Therefore, the Swiss and African tissues analyzed appear to have a bit less lead than do those from other areas. This difference also held for lung tissue.

Immediate sources of lead in wild animals apparently lie in foliage and seeds. Remote sources from forests are probably not the result of industrial contaminants,* but more likely of natural lead in soil. The upper lithosphere has an average lead concentration of 16 ppm., most of it unavailable to plants.[25] The absence of lead in the fertilizers examined suggests that both natural lead, and, in locations contaminated by exhaust fumes from leaded gasoline, airborne lead, may be the remote sources in vegetables and other foods to which domestic animals and man are exposed. Unlike cadmium,[9] probably little or no lead was transferred to food from these fertilizers.

Man has been exposed to lead from the beginning of the age of metals. During the time of the Roman Empire, water pipes and cisterns were made of lead (in Pompeii, for example), and lead vessels were in common use. Lead oxide has been the principal white pigment of paint for over 2,000 years. It is not known whether exposures from all sources have decreased or increased during the past 100 years; waterborne lead from piping has virtually disappeared in this country, but airborne lead almost certainly has increased. Direct contact of

*In suburban areas of Connecticut, considerable lead has been found in juniper bark (25-50 ppm.), shrubs (50-100 ppm.), soil (25 ppm.), yew, and turf from a golf green (10-50 ppm.), presumably from spray residues or gasoline fumes.[23]

lead with foods has lessened owing to government standards. It was impossible to estimate from our data, in these days of tractors and leaded gasoline, the proportion of natural as compared to industrial lead in food.

In 1949, Monier-Williams [6] wrote: "If we assume that lead at these low levels of intake, is absorbed from food as readily as it is from water, we arrive at 0.8 mg. as a safe lead intake from all sources, 1.15 mg. as the maximum permissible and 1.50 mg. as a dangerous intake. Admittedly this estimate is based on a number of assumptions and approximations, but if it is sound it indicates that a total lead intake of roughly 1 mg. daily is the maximum permissible." Kehoe considers 0.6 mg. as the upper limit,* with twice that amount probably injurious in 10 years or more.[17,34]

In the lithosphere and biosphere lead has a great affinity for sulfur, being more strongly chalcophile than many metals of biologic interest.[25] It displaces copper from the sulfhydryl groups of bovine serum albumin,[26] for example. It is also a lithophile element, its ionic radius making it possible for lead to displace potassium, strontium, barium, and, in certain minerals, calcium in carbonates and phosphates.[25] It has been implicated, and discounted, as a cause of many chronic diseases, including hypertension and atherosclerosis; the voluminous work on the toxicity of lead has usually failed to prove it a culprit, although hypotheses are legion.

In one condition, however, toxic amounts of lead have apparently led to disease after recovery from toxicity. Henderson in Queensland described the curious coincidence of plumbism in childhood (from paint) followed decades later by chronic nephritis leading to uremia.[30] The kidneys showed a characteristic pathologic pattern apparently secondary to loss of renal substance, which was unlike any of the known renal diseases. Danilovic has reported similar cases of chronic nephritis confined to a small area in Yugoslavia; the source of lead was in a millstone where local grain was ground.[31] Porritt has called attention to the correlation between lead water pipes and toxemia of pregnancy in England and Wales.[32] That a metallic insult to an organ in childhood may cause apparently irreversible changes leading to death many years later is of considerable interest to the hypothesis that certain "abnormal" trace metals may influence chronic disorders in man.

From our data it would appear that the daily amounts usually ingested by American adults are much lower than the limits set by Monier-Williams and by Kehoe, unless foods high in lead are chosen,† and that they seldom approach or exceed the values which have been considered eventually harmful. Whether or not the lead accumulating in tissues is in inactive "depots" or exerts biologic activity is unknown, as are the lifetime effects of these relatively small amounts.

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*Regulations under the Food, Drug and Cosmetic Act of Connecticut set limits in food at 7 ppm.,[23] an amount which would almost surely cause chronic plumbism if applied to all food.

†Warren and Delavault have analyzed several English and Canadian vegetables from a variety of locations for lead by chemical methods.[33] Many of his values are higher than ours, especially when the vegetables were grown near highways. Some samples of potatoes, for example, had 3 to 12 ppm., of oats 1 to 6 ppm., and of brassicas 1 to 3 ppm. This much lead in food would exceed the "safe" limits for human tolerances. Geographic differences in the lead content of vegetable foods require further investigation.

Larger quantities may be regularly ingested, however, in certain local areas affected by natural or industrial lead in soil or water.

SUMMARY AND CONCLUSIONS

1. The concentrations of lead in a variety of foods, tissues, vegetation, and manufactured products were measured by a microanalytic chemical method and data on human tissues obtained by spectrographic methods were analyzed statistically.

2. Lead seems to be ubiquitous.

3. Lead accumulates with age in the American human kidney, liver, lung, bone, pancreas, and aorta up to the fifth or sixth decade.

4. No obvious increase in exposure from foods or fluids during the past 20 years was demonstrated, although airborne lead has probably increased. This latter increment to the total body burden is usually small.

5. Wild animals and birds are exposed to lead.

6. Lead is probably not an essential element.

7. Lead in human tissues appears to come both from natural sources and from industrial contaminants, although the proportions from each source could not be estimated.

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OBSERVATIONS ON THE IMMEDIATE PROGNOSIS OF ACUTE MYOCARDIAL INFARCTION

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THE long-term prognosis for a patient surviving an acute myocardial infarction and free of serious complications during the first month of convalescence is relatively good.[1] Outcome can be predicted with reasonable accuracy in patients alive and free of serious cardiac complications or congestive heart failure two weeks after sustaining an acute myocardial infarction.[2] Prognosis is most uncertain during the critical first two weeks following infarction, largely because of the unpredictable complications of thromboembolism, arrhythmias, and myocardial rupture. Clinically "mild" cases may suddenly die and patients seriously ill on admission may survive the critical period and enjoy a benign convalescence. Since less stringent management programs have been suggested for so-called mild cases, criteria for prognosticating the course at the onset of infarction are of more than academic interest.

Estimates of outcome on purely clinical grounds leave something to be desired. Halpern and others indicated that their initial prognosis required reversal after the first 24 hours in 29% of 107 cases.[3] Other authors have suggested that laboratory criteria such as white blood cell counts in excess of 15,000 per cmm.,[4] peak serum glutamic oxaloacetic transaminase levels in excess of 350 units,[5] and peak or prolonged temperature elevations are indicative of a poor prognosis. Such laboratory criteria, reflecting the extent of muscle necrosis, imply that the size of the infarcted area is the important prognostic determinant. However, deaths from relatively small infarctions affecting the conduction system of the heart and sudden deaths with little anatomic evidence of muscle necrosis suggest that the nonspecific indicators of tissue destruction offer little prognostic help in these cases.

The following study was accomplished to determine prognostic factors in patients who did well, poorly, or failed to survive the first 30 days following an acute myocardial infarction.

MATERIAL AND METHODS

The records of 350 cases of acute myocardial infarction admitted to the Hartford Hospital during a 20 month period were analyzed. Each case had a history and clinical course compatible with recent infarction of the heart. In addition, each case had electrocardiographic or autopsy evidence of recent infarction. All cases had serial determinations of serum glutamic oxaloacetic transaminase (SGOT) for at least 5 days following hospitalization, unless death occurred before the fifth day. However, elevated transaminase levels were not used as a criterion for establishing the diagnosis of myocardial infarction in the cases studied.

The immediate mortality period was arbitrarily set at 30 days following hospitalization.

Each case was classified into one of the following 3 categories:

1. Uncomplicated: Those cases, alive 30 days following infarction, demonstrating no major complications between the third and thirtieth day of hospitalization.

2. Complicated: Those cases alive at 30 days and having one or more of the following major complications between the third and thirtieth days: (A) shock requiring treatment, (B) congestive heart failure or pulmonary edema, (C) significant cardiac arrhythmias requiring treatment, (D) significant recurring anterior chest pain requiring narcotics, or (E) thromboembolic phenomena.

3. Dead: Those patients who died during the 30 day immediate mortality period.

RESULTS

Classification and Mortality (Table I).—

Uncomplicated: There were 212 patients who survived the immediate mortality period of 30 days and demonstrated a benign clinical course from the third to the thirtieth day following acute myocardial infarction. A history of one or more previous myocardial infarctions was obtained for 49 of these patients. There were 43 second infarctions and 6 third attacks. Therefore, 23 per cent of patients having a benign course had sustained previous cardiac infarction.

Complicated: Sixty-eight patients alive at the end of the immediate mortality period demonstrated one or more of the 6 major complications between the third and thirtieth day following the acute episode. Of the 68 cases, there were 41 first infarctions, 19 second, 5 third, and 3 who had sustained 3 or more previous infarctions. Therefore, 40 per cent of patients demonstrating a complicated course had previous cardiac infarction.

Dead: There were 70 deaths within the arbitrarily chosen immediate mortality period of 30 days. The over-all mortality rate for the entire series of 350 cases was 20 per cent. Of these 70 cases, there were 38 first infarctions and 30 second infarctions. One patient died after the third and one after the fourth infarction. Therefore, approximately one half (46 per cent) of the deaths occurred in those with previous infarction of the heart.

TABLE I. THIRTY-DAY OUTCOME CLASSIFICATION OF PATIENTS WITH FIRST INFARCTIONS AND THOSE WITH PREVIOUS INFARCTION(S)

INFARCTION	UNCOMPLICATED	COMPLICATED	DEAD
First	163	41	38
Second	43	19	30
Third	6	5	1
Fourth or more	0	3	1
Total	212	68	70
Per cent with previous infarction	23	40	46

Twenty-six patients (37 per cent) died during the first 72 hours of hospitalization. A total of 40 patients (57 per cent) died during the first seven days after admission. Fifteen patients (21 per cent) died during the second week following admission, 9 patients, during the third week, and the remainder, during the fourth week.

Fifty autopsies were obtained, each confirming the diagnosis of recent infarction of the heart. In addition, two of these patients showed evidence of recent pulmonary embolism (death on fifth and twentieth day), 4 had myocardial rupture with hemopericardium, 2 demonstrated rupture of papillary muscle, and one patient demonstrated a coronary artery embolus.

Age and Sex Distribution.—There were 253 males and 97 females in the series representing a sex ratio of 2.4 males to 1 female. The age distribution ranged from 28 to 95 years. Of the females, 83 per cent (81/97) were over 60 years of age, whereas only 44 per cent (111/253) of the males were 60 years of age or older (Fig. 1).

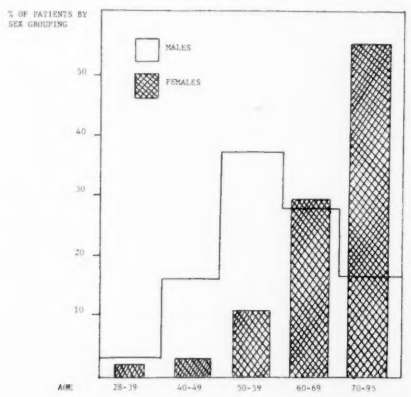

Fig. 1.

The two youngest patients in the series were females; one a 28-year-old juvenile diabetic patient who died after her second myocardial infarction, and the other, a 30-year-old female with familial hypercholesterolemia and a history of angina pectoris who survived her first infarction.

Significant Past History.—In order to assess the significance of factors favoring the development of coronary artery disease or impairing the ability of the heart to withstand the insult of myocardial infarction, each patient was given a rating patterned after the Pathologic Index Rating of Schnur,[6] but modified to a point system. One point was scored for each of the following eight features in the history: (1) Angina Pectoris, (2) Previously documented myocardial infarction, (3) Previous episodes of congestive heart failure, (4) Significant cardiac arrhythmias requiring treatment, (5) Hypertension, (6) Diabetes mellitus, (7) Thromboembolic episodes, and (8) Hypercholesterolemia.

Angina pectoris: There were 98 patients in this series with a past history of angina pectoris, either alone or associated with one or more of the other significant historical factors (Table II).

TABLE II. THIRTY-DAY OUTCOME CLASSIFICATION OF PATIENTS WITH A PREVIOUS HISTORY OF ANGINA PECTORIS

HISTORY	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	PER CENT MORTALITY
Angina pectoris alone	21	5	8	34	24
Angina pectoris plus one or more significant historical factors	27	10	27	64	42
Total cases of angina pectoris	48	15	35	98	36
Total no. cases studied	212	68	70	350	
Per cent with angina pectoris	23	22	50	28	

This represents an incidence of 28 per cent for the series. The incidence of angina pectoris was 23 per cent in the uncomplicated (48/212), and 22 per cent in the complicated (15/68) groups. Of the 70 deaths in the series, 50 per cent (35/70) had a past history of angina pectoris; however, only 8 of these patients had a history of angina pectoris alone. The remaining 27 gave a history of one or more significant associated historical factors.

One half of the patients with a history of angina pectoris had an associated history of previous myocardial infarction, congestive heart failure, or both.

The ominous prognostic implications of angina pectoris seem evident, but the immediate mortality rate of those patients having a history of angina pectoris alone, was only slightly higher than the base-line 20 per cent mortality rate for the total series. However, 65 per cent of patients with a history of angina pectoris had additional significant histories of previous infarctions, arrhythmias, congestive heart failure, or combinations of these.

Previous myocardial infarction: There were 108 patients with a past history of previous myocardial infarction, representing an incidence of 31 per cent of the total cases studied. The over-all mortality rate of this group was 30 per cent. Of the total dead group of 70 patients for the entire series, 46 per cent had a past history of previous myocardial infarction (Table III).

Of 36 patients whose only significant past history was that of previous myocardial infarction there were 6 deaths (mortality rate, 17 per cent) compared

TABLE III. THIRTY-DAY OUTCOME CLASSIFICATION OF PATIENTS WITH A HISTORY OF PREVIOUS MYOCARDIAL INFARCTION

HISTORY	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	PER CENT MORTALITY
Previous infarction only	20	10	6	36	17
Previous infarction plus one or more significant historical factors	29	17	26	72	36
Total patients with previous infarction	49	27	32	108	30
Total cases studied	212	68	70	350	
Per cent with previous infarction	23	40	46	31	

to the 26 deaths (mortality rate, 36 per cent) in the group of 72 patients who had other significant historical features in addition to previous myocardial infarction.

History of congestive heart failure: A prior history of congestive heart failure requiring treatment was obtained in 37 cases, representing an over-all incidence of 11 per cent for the series. The mortality rate for these 37 cases was 43 per cent (16/37). Only 3 cases had no prior history of one or more of the significant associated factors, such as previous infarction, angina pectoris, etc. This is not surprising since congestive heart failure implies the presence of underlying cardiac disease (Table IV).

TABLE IV. THIRTY-DAY OUTCOME CLASSIFICATION OF PATIENTS WITH A HISTORY OF PREVIOUS CONGESTIVE HEART FAILURE

HISTORY	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	PER CENT MORTALITY
Congestive heart failure only	3	0	0	3	0
Congestive heart failure plus one or more significant historical factors	5	13	16	34	47
Total patients with congestive heart failure	8	13	16	37	43
Total patients studied	212	68	70	350	
Per cent with congestive heart failure	4	20	23	11	

Other factors:

Hypertension: Of 55 patients who had a clear history of hypertension requiring treatment, 31 had an associated history of angina pectoris, myocardial infarction, congestive heart failure, or combinations of these factors. Since the prognosis was more likely to be related to these more serious late effects of prolonged hypertension, no attempt was made at classification of these cases into outcome groups. Of 24 patients whose only significant past history was that of hypertension, 5 had a complicated course, and 4 deaths occurred. Because of the small number of patients, no conclusions could be drawn from the mortality rate of 17 per cent (4/24).

Diabetes: There were 34 known diabetic patients in the series, of whom 11 died (mortality rate, 32 per cent). Twelve cases had an associated history of one or more of the factors of angina pectoris, previous infarction of the heart, or congestive heart failure. No conclusions were drawn from the remaining 22 cases because of the small number of patients.

Hypercholesterolemia and thromboembolic episodes: Only 3 cases had a prior history of known hypercholesterolemia and 5 cases had a history of previous thromboembolic episodes. All of these patients survived.

Physical Examination on Admission.—Four major complicating physical findings, occurring during the first 48 hours of hospitalization, were analyzed by group classification and mortality rate.

Shock requiring treatment with vasopressor agents: Fifty-two patients were in a state of significant shock on admission or developed shock within 48 hours after admission. This represents an incidence of 15 per cent for the entire series. There were 27 deaths in this group representing 39 per cent of the total dead group in the series. The mortality rate for the 52 cases having significant shock during the first 48 hours after admission was 52 per cent (27/52). Cases demonstrating shock as the sole physical complication at the time of admission had a significantly higher mortality rate than the base-line mortality rate for the total series (42 per cent vs. 20 per cent). Over one half of the patients exhibiting shock had additional significant physical findings (Table V). The serious prognostic implication of associated shock with acute myocardial infarction has been repeatedly

TABLE V. THIRTY-DAY OUTCOME CLASSIFICATION IN RELATION TO SIGNIFICANT PHYSICAL COMPLICATIONS AT ONSET OF ATTACK

PHYSICAL FINDINGS AT ADMISSION	UNCOMPLICATED	COMPLICATED	DEATH	TOTAL	PER CENT MORTALITY
Shock alone	11	3	10	24	42
Shock plus one or more physical complications	6	5	17	28	60
Total	17	8	27	52	52
Per cent incidence for total series	8	12	39	15	
Arrhythmia alone	11	6	3	20	15
Arrhythmia plus one or more physical complications	5	19	13	37	35
Total	16	25	16	57	28
Per cent incidence for total series	7	38	23	16	
Congestive heart failure alone	6	7	8	21	38
Heart failure plus one or more complicating physical factor	6	13	21	40	52
Total	12	20	29	61	48
Per cent incidence for total series	6	30	41	28	
Persistent pain alone	1	4	4	9	44
Persistent pain plus one or more significant physical complications	2	7	6	15	40
Total	3	11	10	24	42
Per cent incidence for total series	1	17	14	7	

emphasized. It is of interest that 17 of 52 patients with shock (33 per cent) had an uneventful hospital course after the first 48 hours of hospitalization.

Significant arrhythmias (atrial flutter, atrial fibrillation, ventricular tachycardia, and frequent ventricular premature contractions requiring treatment): Arrhythmias were demonstrated in 57 patients during the first 48 hours of hospitalization, representing an incidence of 16 per cent for the series. The mortality rate for this group was 28 per cent (16/57). Only 3 deaths occurred in the 20 cases demonstrating a significant arrhythmia as the sole complicating factor. The remaining 13 deaths occurred in patients having one or more of the other major physical complications in addition to cardiac arrhythmias. Thirty-eight per cent (25/66) of patients demonstrating a complicated clinical course had a significant arrhythmia on admission.

Pulmonary edema and congestive heart failure: There were 61 patients in the series who demonstrated signs of pulmonary edema or congestive heart failure, requiring treatment, during the first 48 hours after hospitalization. This represents an incidence of 28 per cent for the total series (Table V). Twenty-nine deaths occurred in this group (mortality rate 48 per cent). Of the total dead group in the series 41 per cent had significant congestive heart failure or pulmonary edema at the onset of illness.

Approximately two thirds of the cases in this group had one or more major associated physical findings on admission, of which the most common was a significant arrhythmia. However, 21 patients had only congestive failure or pulmonary edema and, of these, 8 died (40 per cent mortality rate), suggesting the major importance of congestive failure in the high mortality rate of this group.

Persistent pain for more than 24 hours after admission not relieved by narcotics: Twenty-four patients had a pattern of persistent pain, despite administration of narcotics, for more than 24 hours after admission representing an incidence of 7 per cent for the series. In this group there were 10 deaths (41 per cent mortality rate). Nine patients had persistent pain as the only major complication, and 4 deaths occurred in this group.

Prognostic Index Rating.—A rating system was devised in an effort to evaluate the relative prognostic importance of the past history and the presence or absence of significant physical complications at the onset of acute myocardial infarction (Table VI). In order to eliminate prejudging of the relative order of importance of these various factors, only one point was scored for each item, rather than a weighted scoring system such as that of Schnur's Pathologic Index Rating.[6] The groupings, by points, were then compared with the over-all base-line mortality rate of 20 per cent for the entire series.

A history of previous myocardial infarction, angina pectoris, or congestive heart failure was classified as Major History, since these factors implied a previously diseased heart. The factors of hypertension, diabetes, hypercholesterolemia, and previous thromboembolic episodes were grouped as Minor History, since their effect on cardiac status was only indirect.

Table VI indicates that those patients with no significant past history and no major complications at the onset of infarction had a significantly lower mortality rate (3 per cent) than for the series as a whole (20 per cent).

TABLE VI. RELATION OF MORTALITY RATES TO HISTORICAL FACTORS AND PHYSICAL COMPLICATIONS ON ADMISSION

	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	PER CENT MORTALITY
No history or physical factors	83	10	3	96	3
Minor history only	22	5	1	28	3.5
Major history only	42	10	4	56	7
Physical only	16	11	7	34	20
Major and minor history only	22	3	6	31	19
Minor history plus physical factors on admission	8	4	4	16	25
Major history only plus physical factors on admission	14	15	23	52	44
Major and minor history plus physical factors on admission	5	10	22	37	60
All patients with major history plus physical complications	19	25	45	89	50

Those cases with only a Minor History had a similar low mortality rate (3.5 per cent), belying the usual importance ascribed to these factors in prognosis.

The mortality rate of 56 patients with a Major History was only 7 per cent, considerably lower than expected in light of previous reports of the serious prognostic implications of these factors.

Those cases with physical complications on admission, without a significant Major or Minor History, had a mortality rate of 20 per cent. Those with a Major and Minor History only had a mortality rate of 19 per cent; and those with a Minor History plus physical complications had, as expected, a mortality rate approaching that of the cases with physical complications only (25 per cent).

Those patients with both a significant Major History and physical complications demonstrated a significantly higher mortality rate (50 per cent).

One point was scored for each factor in the Minor or Major past history, or physical complication after admission to the hospital. Table VII indicates the progressive increase in mortality rate as the score increased. The specific factors involved seemed of less importance than the accumulated total number or either historical or physical factors after admission, or their combinations. Of 287 patients whose score was 3 or less, the over-all mortality rate was 12 per cent. Of 62 patients scoring 4 or more points, the over-all mortality rate was 57 per cent.

Body Temperature.—The limits of normal body temperature were considered to range from 98.0°F. to 100.0°F. by rectal thermometer. The maximum temperature rise during the first week following hospitalization was recorded, and compared with the outcome classification (Table VIII). For 145 cases with a maximum termperature rise not exceeding 100.0°F., the mortality rate was 16 per cent. Of 205 cases in whom the maximum temperature rise exceeded 100.0°F., the mortality rate was 23 per cent. There was no significant difference between the group whose maximum temperature ranged from 100.1 to 102.0°F. and the group whose maximum temperature exceeded 102.0°F. In patients manifesting fever, the height of the temperature elevation afforded no specific

TABLE VII. PROGNOSTIC INDEX SCORING IN RELATION TO MORTALITY RATES

SCORE	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	PER CENT MORTALITY
0	83	10	3	96	3
1	60	11	8	79	10
2	41	21	12	74	16
3	19	8	11	38	29
4	5	11	17	33	51
5	2	6	11	19	58
6	1	1	6	8	75
7	1	0	2	3	67
Total no. cases	212	68	70	350	
Score 0–3	203	50	34	287	12
Score 4–7	9	18	36	63	57

prognostic help. Patients demonstrating subnormal body temperatures had a slightly higher mortality rate than the base-line 20 per cent. However, those patients whose maximum body temperature rise remained within the relatively narrow normal range of 98.0 to 98.9°F. had a significantly lower mortality rate (4 per cent) than for the series as a whole. Maximum body temperatures below 98.0°F. and above 98.9°F. offered no significant prognostic clues.

TABLE VIII. MAXIMUM BODY TEMPERATURE ELEVATION IN RELATION TO MORTALITY RATES

MAXIMUM TEMPERATURE RISE	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	PER CENT MORTALITY
Below 98.0° F.	4	0	2	6	33
98.0° to 98.9°	44	9	2	55	4
99.0° to 99.9°	55	10	19	84	23
Total 100.0° and below	103	19	23	145	16
100.1° to 101.0°	47	21	20	88	23
101.1° to 102.0°	39	18	18	75	24
102.1° to 105.0°	23	10	9	42	22
Total 100.1° and above	109	49	47	205	23

Erythrocyte Sedimentation Rate (ESR): The Westergren method (Normal range 0 to 20 mm./hr.) was used to determine the ESR in 335 patients. After the first 200 cases in this series were analyzed, it was noted that the maximum ESR elevation occurred in nearly one fourth of the cases after the second week. Therefore, the maximum ESR value obtained during the first 30 days of the hospital course was recorded for the 335 patients in whom this determination was available. As illustrated in Table IX, there was little or no difference in the outcome classification or mortality rate in the group showing a normal ESR compared to the groups showing various degrees of ESR elevations. Nine patients, in whom the maximum ESR rise exceeded 100 mm./hr., demonstrated a 45 per

cent mortality rate, but this small number represents less than 3 per cent of 335 patients studied. The mean 30 day maximum ESR for 275 patients, alive at the end of 30 days following infarction, was 38 mm./hr. Of 60 patients who died within this immediate mortality period, the mean 30 day maximum ESR was 40 mm./hr.

TABLE IX. MAXIMUM ERYTHROCYTE SEDIMENTATION RATES IN RELATION TO MORTALITY RATES

ERYTHROCYTE SEDIMENTATION RATE (WESTERGREN)	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	PER CENT MORTALITY
Normal—20 mm./hr. or less	65	18	19	102	19
21 to 39 mm./hr.	51	14	12	77	16
40 to 59 mm./hr.	44	12	12	68	18
60 to 79 mm./hr.	30	10	8	48	17
80 to 99 mm./hr.	15	11	5	31	16
100 mm./hr.	3	2	4	9	45
Total	208	67	60	335	

White Blood Cell Count.—The maximum white blood cell count recorded during the 30 day immediate mortality period was recorded in 344 cases and compared with the outcome classification and mortality rate (Table X).Forty-two per cent of the patients (146) had a white blood cell count of less than 10,000/cu.mm. and an 18 per cent mortality rate. Those with a white blood cell count of 15,100 to 20,000 had a 40 per cent (21/52) mortality rate and those above 20,000/cu.mm., a mortality rate of 43 per cent. It would appear that a normal maximum white blood cell count, i.e., less than 10,000/cu.mm. is associated with a lower mortality rate, but that an elevated white blood cell count of over 15,000/cu.mm. had much the same significance as one over 20,000/cu.mm. This suggests that a normal white blood cell count has a favorable prognostic implication, and that an abnormally elevated count suggests a less favorable outcome, regardless of the degree of elevation.

Serum Glutamic Oxaloacetic Transaminase (SGOT).—All patients accepted for study in this series had at least 5 serial determinations of the SGOT from the time of admission unless death occurred before the sixth day. SGOT determinations were done by the Karmen spectrophotometric method (normal 10-50 units). Table XI illustrates the relationships between the maximum SGOT rise, outcome classification, and mortality rates. Those patients with a peak transaminase of less than 100 units had a mortality rate of 11 per cent (14/128). Those with a peak transaminase exceeding 300 units demonstrated a 60 per cent mortality rate (21/60). However, 38 of the 60 cases, whose peak transaminase exceeded 300 units, manifested shock, significant arrhythmias, congestive heart failure, or combinations of these findings. The mortality rate of this group was 47 per cent (18/38). Of the 22 cases whose peak transaminase levels exceeded 300 units, but showed no evidence of shock, arrhythmias, or congestive heart failure at the time of admission, there were 3 deaths. The mortality rate for this group was

TABLE X. MAXIMUM WHITE BLOOD CELL COUNTS IN RELATION TO MORTALITY RATES

WHITE BLOOD CELL COUNT	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	PER CENT MORTALITY
Normal—less than 10,000/cu. mm.	107	24	15	146	10
10,000 to 15,000/cu. mm.	81	27	24	132	18
15,100 to 20,000/cu. mm.	18	13	21	52	40
20,100 to 25,000/cu. mm.	4	2	3	9	
Over 25,000/cu. mm.	1	1	3	5	43
Total	211	67	66	344	
15,000 or less/cu. mm.	188	51	39	278	14
15,000 to 25,000 plus/cu. mm.	23	16	27	66	41

TABLE XI. PEAK SGOT VALUES IN RELATION TO MORTALITY RATES

SGOT PEAK VALUES	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	PER CENT MORTALITY
Below 100	96	18	14	128	11
101–200	55	17	18	90	20
201–300	39	16	17	72	23
301–350	13	6	5	24	21
Over 350	9	11	16	36	44
Total	212	68	70	350	
Total cases over 300	22	17	21	60	35
Unassociated with complications	14	5	3*	22	14
Associated with shock, arrhythmia, or congestive failure	8	12	18	38	47

*Deaths occurred on days 1, 4, and 5.

14 per cent (3/22); considerably lower than the base-line 20 per cent mortality rate for the entire series.

Peak transaminase values greater than 350 units have previously been considered of ominous prognostic significance. Of 36 cases in this series in whom the peak SGOT exceeded 350 units, there were 16 deaths (44 per cent mortality). The mean SGOT value for this group was 457 units with a range of 356 to 940 units. Shock, arrythmia, congestive heart failure, or combinations of two or more of these findings were present at the onset of symptoms in 23 of the cases. Thus 64 per cent (23/36) of patients with a peak SGOT elevation greater than 350 units had one or more of the major complicating physical factors usually associated with an increased mortality and capable of contributing to the elevated SGOT measurement. Thirteen of the 16 deaths occurred in this group (81 per cent of deaths). Thus, the poor prognosis said to accompany SGOT elevations of greater than 350 units would seem to apply to those cases with a potentially higher mortality rate because of shock, arrhythmia, and congestive

heart failure. In the cases uncomplicated by these factors, three deaths occurred in 13 patients with SGOT greater than 350 units (23 per cent).

Fasting Blood Sugar.—The fasting blood sugar was determined in 293 patients within 48 hours following admission (Table XII). Blood sugar determinations were done by the Folin-Wu method (Normal 80-120 mg. per cent). Values over 125 mg. per cent were considered as definitely abnormal. The base-line mortality rate for this group was 20 per cent (60/293). There were 34 known diabetic patients or patients proved to have clinical diabetes mellitus before discharge. Of the 259 nondiabetic patients, 157 (61 per cent) demonstrated a normal fasting blood sugar during the first 48 hours after admission. The mortality rate for this group was 12 per cent. In contrast, the mortality rate for the remaining 102 nondiabetic patients who demonstrated abnormal elevations of the fasting blood sugar (range 126-198 mg. per cent) was 30 per cent. The known diabetic patients demonstrated a 32 per cent mortality rate (11/34). Although it has previously been suggested that hyperglycemia following acute myocardial infarction indicates latent diabetes,[7] it seems unlikely that over one third (39 per cent) of 293 patients were latent diabetics. An elevated fasting blood sugar following acute myocardial infarction in nondiabetic patients appears to contribute to an ominous prognosis.

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TABLE XII. FASTING BLOOD SUGAR VALUES IN RELATION TO MORTALITY RATES IN DIABETIC AND NONDIABETIC PATIENTS

FASTING BLOOD SUGAR	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	PER CENT MORTALITY
Normal—70–125	118	21	18	157	11
Abnormal—126–198	48	23	31	102	30
Known diabetic	17	6	11	34	32
Total	183	50	60	293	20
Total patients with abnormal blood sugar	65	29	42	136	31

Serum Cholesterol.—Serum cholesterol determinations were accomplished within one week of admission in 174 patients (Table XIII). The base-line mortality rate of this group was 16 per cent (28/174). The upper limit of normal for serum cholesterol, by the Bloor method, in our laboratory is 280 mg. per cent. However, the range of serum cholesterol from 280-320 mg. per cent is considered equivocal by many clinicians, and only those values of 320 mg. per cent or greater were considered definitely abnormal. As illustrated in Table XIII, there appeared to be no relationship between the level of serum cholesterol, outcome classification, or mortality rate for these 174 patients.

Complications From the Third to the Thirtieth Day Following Admission.—The most common complication occurring in the 68 cases classified as having a complicated course, but alive at the end of 30 days, was congestive heart failure alone or associated with a significant arrhythmia. There were 26 cases (38 per cent)

TABLE XIII. SERUM CHOLESTEROL VALUES IN RELATION TO MORTALITY RATES

SERUM CHOLESTEROL (MG. %)	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	PER CENT MORTALITY
Normal—180–279	44	8	9	61	15
Equivocal—280–319	29	8	8	45	18
Abnormal—320 or over	42	15	11	68	16
Total	115	31	28	174	16
Total cases—over 280	71	23	19	113	17

of congestive heart failure, nine of which were associated with a significant arrhythmia. Recurrent severe anterior chest pain suggesting extension of infarction occurred in 15 patients, thromboembolic phenomena in 6 patients, and shock requiring treatment with vasopressor agents in 8 patients.

Thirty-six of the 70 patients classified in the dead group (51 per cent) had one or more major complications prior to death. Congestive heart failure associated with recurrent severe anterior chest pain suggesting extension of the infarction developed in 17 patients and recurrent shock in 8 patients. Six patients had evidence of a second infarction during the immediate mortality period and one patient had evidence of pulmonary embolism.

Anticoagulant Therapy.—Of the 350 cases studies, 274 (78 per cent) received anticoagulants of the coumarin variety. No patients were treated with heparin. Good anticoagulant control was arbitrarily defined as prothrombin activity of 25 per cent or less (20 seconds or more) for at least 4 of every 7 days, and establishment of therapeutic levels within the first 5 days following infarction. Using these criteria, 155 cases (57 per cent) of the anticoagulant-treated group were classified as being under good control. The incidence of thromboembolism in this group was 3.2 per cent (5 cases) and the over-all mortality rate of the group was 14.2 per cent (Table XIV). Of the 119 patients classified as being under poor anticoagulant control, none had thromboembolic phenomena. The over-all mortality rate for this group was 5.1 per cent.

A total of 76 cases in the entire series received no anticoagulant therapy. The mortality rate for this group was 55 per cent (42/76), and the incidence of thromboembolism was 3.9 per cent (6/76). However, more than three fourths of the patients who died without receiving anticoagulant therapy, died within the first 7 days after admission (33/42), and over one half (26/42) died within the first 72 hours. Therefore, for purposes of comparison, if these 33 cases are eliminated because death occurred too soon for adequate anticoagulant therapy, the mortality rate for 43 patients receiving no anticoagulants and surviving the first week after infarction was 21 per cent (9/43). Only one fatal embolus occurred in this group.

Bleeding as a complication of anticoagulant therapy occurred in three patients in the good-control group, representing an over-all incidence of 2 per cent for the anticoagulant-treated cases.

TABLE XIV. THIRTY-DAY OUTCOME CLASSIFICATION AND MORTALITY RATES IN RELATION TO ANTICOAGULANT THERAPY

ANTICOAGULANTS	UNCOMPLICATED	COMPLICATED	DEAD	TOTAL	THROMBOEMBOLISM (%)	PER CENT MORTALITY
Good control	105	28	22	155		14.2
Thromboembolism		(2)	(3)	(5)	3.2	
Bleeding		(2)	(1)	(3)		
Poor control	88	25	6	119		5.1
Thromboembolism		(0)	(0)	(0)	0	
Bleeding		(0)	(0)	(0)		
No anticoagulants	19	15	42	76		55
Thromboembolism		(2)	(1)	(3)	3.9	
Total cases	212	68	70	350		20
Thromboembolism		(4)	(4)	(8)	2.3	
Bleeding		(2)	(1)	(3)		

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SUMMARY AND CONCLUSIONS

The records of 350 patients with acute myocardial infarction were analyzed to determine if any features of the past medical history, physical examination, or laboratory studies were of specific value in predicting the immediate outcome and course during the first 30 days following infarction.

1. There were 70 deaths within the first 30 days following the onset of myocardial infarction, representing a 20 per cent base-line mortality rate for the entire group.

2. The immediate mortality rate was significantly higher than the base-line mortality rate in the following circumstances:

(A) A previous history of congestive heart failure (43 per cent mortality rate), angina pectoris (36 per cent), and previous myocardial infarction (30 per cent). However, when either of the latter two were the sole significant item in the past history, the mortality rate was not significantly different from the base-line mortality rate.

(B) The presence of shock at the onset of the acute episode (52 per cent), congestive heart failure (47 per cent), or persistent pain unrelieved by narcotics for more than 48 hours (41 per cent).

(C) A prognostic index score of 4 points or more, regardless of whether the points represented significant historical factors or physical complications at the onset of the acute episode.

3. A peak serum glutamic oxaloacetic transaminase (SGOT) level of 350 units or more was associated with a significantly higher mortality rate than the base-line 20 per cent. However, those cases not associated with shock, congestive heart failure, or cardiac arrhythmias, who demonstrated peak SGOT values greater than 300 units, had a lower mortality rate than the base line for the series

as a whole (14 per cent). The ominous prognostic significance usually ascribed to peak SGOT levels in excess of 350 units therefore seems to represent an indirect way of stating that shock, arrhythmia, and congestive heart failure worsen the prognosis. Those patients with peak SGOT levels of less than 100 units had a significantly lower mortality rate (11 per cent) than the base-line mortality rate for the total series.

4. A maximum white blood cell count of greater than 15,000/cu.mm. was associated with a significantly higher mortality rate (41 per cent), but the degree of elevation of the white cell count above this figure afforded little additional prognostic help. A normal white cell count was associated with a significantly lower mortality rate (10 per cent) than for the series as a whole.

5. A normal body temperature between the relatively narrow limits of 98.0 to 98.9°F. was associated with a significantly lower mortality rate (4 per cent) than for the series as a whole. Maximum body temperature elevations above 98.9°F. or subnormal body temperatures afforded no significant prognostic help.

6. Erythrocyte sedimentation rates and serum cholesterol levels afforded no useful prognostic information.

7. Nondiabetic patients with abnormally high fasting blood sugar levels within the first 48 hours after hospital admission demonstrated a significantly higher mortality rate (30 per cent) than those with normal blood sugar levels (12 per cent).

8. The mortality rate for 119 patients classified as having poor anticoagulant control was considerably lower (5.1 per cent) than that for 155 patients classified as having good control (14.2 per cent); the significance, if any, of this remains obscure. Of 43 patients who survived the first week, but received no anticoagulant therapy, the mortality rate was essentially that of the base-line mortality for the total series.

9. Because of the multiplicity of factors contributing to the degree of seriousness of an acute myocardial infarction no single specific feature of the past medical history, physical complications, or laboratory data affords useful prognostic help. This is especially true of the laboratory criteria. A simple arithmetic scoring of the total number of significant factors in the past history and physical complications at the onset of infarction appears to be as reliable as any other guide to the immediate prognosis of acute myocardial infarction.

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DELAY IN SEEKING REHABILITATION AFTER CEREBROVASCULAR ACCIDENTS

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NEW medical techniques can be more difficult to apply than they are to discover. Widespread acceptance may be slow, particularly when a new therapy has gradual, undramatic results. Rehabilitation of the long-term patient seems to follow this rule. For 15 years, physiatrists have stressed the belief that rehabilitation must begin early to ensure maximum benefit. Despite the emphasis on early care, the prompt applicant to rehabilitation centers is still the exception rather than the rule. For instance, of hemiplegic patients discharged from the Institute of Physical Medicine and Rehabilitation in New York, 45 per cent delayed 6 months or more before starting rehabilitation.[1] Similarly, of cardiac patients from the Altro Workshops in California, 58 per cent delayed 6 months or more before starting rehabilitation[2]; and in Baltimore, Maryland, 24 per cent of stroke patients delayed 1 year or more before applying for rehabilitation, as this paper will show.

Apathy and an unconscious desire to remain invalid are among many reasons which form substantial obstacles to early care. Nevertheless, when the important rule of prompt care is broken so often, it seems possible that the community's understanding of rehabilitation differs greatly from that of the physiatrist. For that reason I wish to test the hypothesis that socioeconomic problems rather than a positive desire for rehabilitation form the major reason for applying to a rehabilitation center in Baltimore. In doing so, this paper will show that the period of delay in seeking rehabilitative care is related to certain characteristics of each patient; these characteristics include age, sex, race, marital and financial status, and severity of disability produced by the disease. Finally, I will compare the actual pattern of delay with the expected pattern if applicants were largely motivated by a positive desire for rehabilitation.

CEREBROVASCULAR ACCIDENTS AS A REHABILITATION PROBLEM

Cerebrovascular accidents (CVAs) caused about 191,000 deaths in the

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United States in 1959, nearly 12 per cent of the death total.[3] They rank third among causes of death, surpassed only by diseases of the heart and malignant neoplasms. Nevertheless, many CVA patients survive the initial episode and live for some years. For example, Robinson and others[4] found that of all patients with cerebral thrombosis who were admitted in recent years to hospitals in Worcester, Massachusetts, 79 per cent survived the initial attack and 50 per cent of the survivors lived more than 4 years. The National Heart Institute has estimated that two million people living in the United States are incapacitated by this group of diseases.[5]

In past years, the physician's choice of treatment for patients with CVA "lay between masterly inactivity and skillful neglect."[6] More recently, however, physical medicine and rehabilitation techniques have developed sufficiently to offer good chances for improvement of disability.[1,7] Lowenthal and others[8] believe that 35 per cent of survivors need such techniques, whereas 65 per cent recover spontaneously and rapidly.

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When rehabilitation measures are delayed, decubitus ulcers, urinary infections, contractures, and other complications may occur to impair the success of rehabilitation. Nevertheless, many long-term patients are slow in seeking adequate care. The problem of delay has been most thoroughly studied in patients with cancer, and has been well reviewed by Kutner and others.[9] However, the pattern of delay in patients with cancer is likely to differ from that in patients with CVA. The unavoidable delay between the biologic start of cancer and the onset of its recognizable symptoms does not usually occur with strokes. Disability is often maximal immediately after the initial episode, and the diagnostic class is rarely in doubt. Both disease groups have this in common, however, that the patient, relatives, or attending physician may be excessively pessimistic over the prognosis once the diagnosis is established, and they may maintain the attitude that the best treatment is to do nothing.

Determining the pattern of how patients delay is a first step in clarifying the reasons for it. In the next section of this paper we describe the pattern of delay for patients with CVA in Baltimore.

THE PATIENTS STUDIED

Montebello Chronic Disease Hospital is the main rehabilitation center for the Baltimore metropolitan area. This hospital gives medical and rehabilitative care to residents of Maryland with a long-term illness. The 612 patients in this study are those who applied for admission to Montebello during 1956 through 1959 and in whom the primary diagnosis was cerebrovascular accident. The information analyzed was obtained from application forms which were filled in by the attending physicians.

The period between onset of illness and receipt of the application in Montebello is termed the period of delay in this paper. This period ranged from an ideal promptness of 3 days to a lamentable delay of more than 10 years. Thirty-seven per cent applied within 4 weeks of onset, whereas 24 per cent delayed 1 year or more. The median period of delay was 8 weeks.

DELAY BY AGE, SEX, AND RACE

Age.—Ages ranged from 27 to 90 years, with a median of 64 years. Table I compares the age of patients with the percentage applying for rehabilitation in each time period after onset of illness. Delay was greatest in the 154 patients between 55 and 64 years of age; of these, 31 per cent applied within 4 weeks, 26 per cent delayed 51 weeks or more, while the median period of delay was 11 weeks. Patients above and below this age range applied more rapidly. Most prompt in applying were 82 applicants, aged 75 years and older, of whom 49 per cent applied within 4 weeks.

TABLE I. DELAY IN APPLYING FOR REHABILITATION, BY AGE OF PATIENT*

AGE (YEARS)	WEEKS BETWEEN ONSET AND APPLICATION (% APPLYING IN EACH PERIOD)					MEDIAN NO. OF WEEKS
	TOTAL	1 TO 4	5 TO 10	11 TO 50	51+	
Under 55	116	33.6	25.0	21.6	12.1	8
55–64	154	30.5	18.8	20.2	26.2	11
65–74	168	39.9	16.7	17.9	25.6	8
75+	82	48.8	14.7	14.6	32.0	5
Total†	531*	37.3	18.6	19.4	24.7	8

*This table excludes 81 applicants whose period of delay was unknown.
†Total includes 11 persons of unknown age.

Sex.—About equal numbers of each sex applied for admission. Table II describes the 530 patients whose period of delay was known. The previously described pattern of delay with age applied to each sex. However, women at all ages consistently delayed less than men. For those 55 to 64 and those 75 and older, the sex difference was small and not significant. Differences were greater for those under 55 and those 65 to 74 years of age; women were significantly more prompt in applying.

Race.—The applicants included 419 whites, 192 nonwhites, and 1 person whose race was not determined (Table III). The pattern for delay with age differed slightly for each race, but, again, persons 55 to 64 years of age delayed longest, whereas those above and below this range applied more promptly. In all age groups, nonwhites applied with the same or less delay than whites. For those 65 years and older, the median delay was 7 weeks for each race. Under 55 years of age, whites delayed for a median period of 9 weeks, and nonwhites 6 weeks; this difference was not significant. In the 96 whites and 58 nonwhites between 55 and 64, however, the median period of delay was 13 and 9 weeks, respectively; this difference was statistically significant.

DELAY BY MARITAL AND PAYMENT GROUPS

Marital Status.—Of 496 applicants of known marital status and known period of delay, 259 were married, 59 were single, 100 were widowed, and 78 were "other," mainly divorced or separated. Table IV relates marital status to period of delay.

TABLE II. DELAY IN APPLYING FOR REHABILITATION, BY AGE AND SEX OF PATIENT*

AGE (YEARS)	SEX	WEEKS BETWEEN ONSET AND APPLICATION (% APPLYING IN EACH PERIOD)					MEDIAN NO. OF WEEKS
		TOTAL	1 TO 4	5 TO 10	11 TO 50	51+	
Under 55	Males	62	25.8	30.6	21.0	22.6	10
	Females	54	40.8	18.5	22.2	18.5	7
55–64	Males	86	30.3	18.6	24.4	26.7	11
	Females	68	29.1	19.1	19.2	30.9	10
65–74	Males	76	28.2	13.2	18.4	30.3	10
	Females	92	41.4	19.6	17.4	21.7	7
75+	Males	42	47.6	16.7	12.3	21.4	5
	Females	40	50.0	12.5	15.0	22.5	4
Total†	Males	270	34.5	19.3	20.0	26.3	9
	Females	260	40.0	25.0	18.8	23.1	8

*This table excludes 82 patients whose period of delay or sex was unknown.
†Totals include 10 patients of unknown age.

TABLE III. DELAY IN APPLYING FOR REHABILITATION, BY AGE AND RACE OF PATIENTS*

AGE (YEARS)	RACE	WEEKS BETWEEN ONSET AND APPLICATION (% APPLYING IN EACH PERIOD)					MEDIAN NO. OF WEEKS
		TOTAL	1 TO 4	5 TO 10	11 TO 50	51+	
Under 55	White	81	32.1	22.2	24.7	21.0	9
	Nonwhite	36	38.9	30.6	11.1	19.4	6
55–64	White	96	28.2	18.8	23.0	30.2	13
	Nonwhite	58	34.5	19.0	20.7	25.9	9
65+	White	190	43.1	14.7	18.4	23.7	7
	Nonwhite	60	41.7	20.0	11.7	26.7	7
Total†	White	371	36.7	17.3	21.3	24.8	9
	Nonwhite	159	38.4	22.0	15.1	24.5	7

*This table excludes 81 applicants whose period of delay was unknown, and 1 patient of unknown race.
†Totals include 9 persons of unknown age.

For those under 65 years, the 162 married applicants delayed longer than other marital groups. The applicants who were married delayed for a median period of 10 weeks, in contrast to 8 weeks for other groups. The pattern differed for applicants 65 years and older in that the 29 single persons delayed longer than married persons, though not significantly so. Again, the 94 married

TABLE IV. DELAY IN APPLYING FOR REHABILITATION, BY AGE AND MARITAL STATUS OF PATIENTS*

AGE (YEARS)	MARITAL STATUS	WEEKS BETWEEN ONSET AND APPLICATION (% APPLYING IN EACH PERIOD)					MEDIAN NO. OF WEEKS
		TOTAL	1 TO 4	5 TO 10	11 TO 50	51+	
Under 65	Married	162	30.3	20.4	22.2	25.9	10
	Single	30	36.6	20.0	26.6	16.7	8
	Widowed	33	30.3	27.3	15.1	27.3	8
	Other	33	39.2	18.2	24.2	18.2	8
65+	Married	94	40.4	20.2	20.2	19.1	7
	Single	29	34.4	20.7	13.8	31.0	8
	Widowed	64	50.0	6.3	21.9	21.9	5
	Other	45	44.5	17.8	8.9	28.9	6
Total†	Married	259	35.2	20.1	21.6	23.2	8
	Single	59	35.6	20.3	20.4	23.7	8
	Widowed	100	43.0	13.0	20.0	33.0	7
	Other	78	42.3	17.9	15.4	24.4	7

*This table excludes 50 applicants whose period of delay was unknown, and 66 applicants of unknown marital status.

†Totals include 6 persons of unknown age.

applicants delayed for a median period of 7 weeks, longer than widowed and "other" persons whose group medians were 5 and 6 weeks, respectively.

Payment Group.—Whenever possible, the patient or his immediate family were asked to pay part of the cost of hospital care. Using written rules, social workers in the Department of Public Welfare estimated the amount to be paid according to the family's income and financial obligations. These financial arrangements were completed for 395 applicants described in Table V. No payment was required from 218 indigent patients. Between $1 and $100 was set as the monthly payment for 94 patients. Few of the 83 patients required to pay $101 or more could cover the full cost of care.

The 136 persons under 65 years, who made no payment delayed significantly less than higher income groups. Of the indigent, 40 per cent applied within 4 weeks of onset of illness, compared with 28 per cent of those who paid $1 to $100, and 24 per cent for those who paid $101 or more. This delay pattern was reversed for those 65 years and older. The 77 indigent applicants were slowest to apply, with a median delay period of 9 weeks, in contrast to 5 and 6 weeks, respectively, for higher payment groups.

DELAY BY SEVERITY OF DISABILITY

The severity of disability is described from two aspects: side of hemiplegia, and a scoring method based on the activities of daily living.

Side of Disability.—In general, right hemiplegics are often unable to speak and are more disabled than left, while those with bilateral involvement are the most severely disabled. For 486 applicants, the side of disability was noted on

TABLE V. DELAY IN APPLYING FOR REHABILITATION, BY AGE AND MONTHLY PAYMENT FOR HOSPITAL CARE*

AGE (YEARS)	MONTHLY PAYMENT	WEEKS BETWEEN ONSET AND APPLICATION (% APPLYING IN EACH PERIOD)					MEDIAN NO. OF WEEKS
		TOTAL	1 TO 4	5 TO 10	11 TO 50	51+	
Under 65	$0	136	39.7	22.1	20.6	17.6	6
	$1–$100	40	27.5	17.5	27.5	27.5	14
	$101 and over	41	24.4	17.1	36.6	22.0	18
65+	$0	77	35.1	18.2	22.1	24.7	9
	$1–$100	52	46.1	19.2	23.1	11.5	5
	$101 and over	42	45.2	14.3	21.5	19.0	6
Total†	$0	218	38.5	20.6	21.1	19.7	7
	$1–$100	94	38.3	18.1	25.5	18.1	8
	$101 and over	83	34.9	15.3	31.7	23.3	11

*This table excludes 216 applicants whose period of delay or monthly payment was unknown.
†Totals include 7 persons of unknown age.

TABLE VI. DELAY IN APPLYING FOR REHABILITATION BY AGE AND SIDE OF DISABILITY*

AGE (YEARS)	SIDE OF DISABILITY	WEEKS BETWEEN ONSET AND APPLICATION (% APPLYING IN EACH PERIOD)					MEDIAN NO. OF WEEKS
		TOTAL	1 TO 4	5 TO 10	11 TO 50	51+	
Under 55	Right	53	43.4	17.0	30.2	9.4	6
	Left	45	28.9	26.7	13.3	31.1	9
	Both	12	25.0	33.3	16.6	25.0	8
55–64	Right	57	35.0	21.1	22.8	21.1	8
	Left	77	28.6	20.8	20.7	29.9	11
	Both	12	16.7	8.3	33.4	41.7	36
65+	Right	103	41.8	17.5	17.5	23.3	7
	Left	96	46.9	16.7	17.7	18.8	5
	Both	25	44.0	12.0	12.0	32.0	7
Total†	Right	217	40.6	18.0	22.6	18.9	7
	Left	219	36.6	20.1	17.8	25.6	8
	Both	50	34.0	16.0	18.0	32.0	11

*This table excludes 126 applicants whose period of delay or side of disability was unknown.
†Totals include 6 persons of unknown age.

the application forms. There were 217 disabled on the right side only, 219 on the left, and for 50, the disability was bilateral. For all applicants, Table VI shows that those affected on the right side delayed least, with a median delay of 7 weeks, compared with 8 weeks for those with hemiplegia of the left side, and 10 weeks for those with bilateral disability.

In applicants under 65 years of age, those with hemiplegia of the right side again delayed least. However, for those aged 65 and over, the 96 left hemiplegics had a median delay of 5 weeks, whereas the 103 right hemiplegics delayed longer with a median of 7 weeks. These differences were statistically significant. At all ages, applicants with bilateral involvement delayed for about the same period or longer than those affected on one side only. These differences were not statistically significant in any one age group.

Disability Score.—Of all 612 applicants, 294 were eventually admitted to Montebello. For the latter, disability on admission was given a numerical value by a scoring method based on the activities of daily living.[10] This disability score gave 100 points to the patient able to care completely for himself, no points to those helpless in bed, and intermediate scores when disability was between these extremes.

TABLE VII. DELAY IN APPLYING FOR ADMISSION, BY AGE AND DISABILITY SCORE*

AGE (YEARS)	DISABILITY SCORE	WEEKS BETWEEN ONSET AND APPLICATION (% APPLYING IN EACH PERIOD)					MEDIAN NO. OF WEEKS
		TOTAL	1 TO 4	5 TO 10	11 TO 50	51+	
Under 55	45–	24	33.3	29.2	29.1	8.3	7
	50+	48	35.4	14.6	25.1	25.0	11
55-64	45–	36	19.5	16.7	27.8	36.1	21
	50+	42	31.0	23.8	28.6	16.7	9
65+	45–	65	33.9	18.5	29.2	18.5	10
	50+	29	51.7	17.2	10.3	20.7	4
Total	45–	125	29.6	20.0	38.8	21.6	11
	50+	119	37.8	18.5	22.7	21.0	8

*Excludes 50 admissions whose period of delay or disability score was unknown.

Table VII analyzes the findings for the 244 admissions whose period of delay and disability score were known. For patients admitted who were aged 55 and older, those whose disability score was 45 or less delayed significantly longer than those whose disability score was 50 or more. In patients under 55 years, the reverse situation was found; 24 with scores of 45 or less delayed a median period of 7 weeks, compared with 11 weeks for the 48 who scored 50 or more.

DISCUSSION OF FINDINGS

Few problems of human behavior are so simple that they can be completely described in terms of a small number of variables. For example, certain variables may have a significant effect on the speed of applying for rehabilitation, but may be canceled by even more potent variables. This situation must be remembered in interpreting this study.

Applicants between 55 and 64 years delayed longest, while younger and older patients applied more promptly. This age pattern occurred in both sexes and both races. Several factors may have combined to produce this effect. On the one hand is the situation that the older the patient, the less likely is the spouse to be alive and able to care for the disabled individual at home. On the other hand, younger patients and their families might be more likely to believe that their condition could be improved. In general, the problem of caring for the older patient physically seemed the more potent factor since the most prompt applicants were those 75 years and older.

At all ages, women delayed less than men. Again, the problem of caring for the patient at home seemed to be the major controlling factor. In younger families, the male wage earner was less likely to undertake the full-time care of his disabled wife. In older families, the wife was less likely to have a husband alive and physically able to provide the needed care. If the major factor had been a positive desire for rehabilitation, one would have expected both sexes to apply with equal promptness.

Nonwhites at all ages applied with the same or less delay than whites. The poorer socioeconomic conditions in which nonwhites live, with inadequate facilities for caring for the long-term patient at home, appear a likely cause for the racial difference.

Single, widowed, and "other" persons who lacked the support of husband or wife, delayed less than married persons of the same age range. The one exception to this statement was single persons over 65 who delayed longer than married persons of the same age. One explanation may be that elderly single persons might have accumulated sufficient savings to pay for nursing care at home for some time, thus delaying their applications until financial problems arose. One can only guess how patients, educated to the value of rehabilitation, might behave in relation to marital status; it might well be that married patients would then delay least because they were encouraged by their spouses to apply early.

Patients in good financial circumstances might be expected to be cared for at home longer than patients from less comfortable homes. This was found true for applicants under 65 years of age, with indigent persons delaying least and high-payment groups delaying most. Applicants 65 years and older did not follow this pattern, and indigent patients delayed most in this age range. Most likely, other factors canceled the effect of income; for example, a greater proportion of the higher payment group may have been widows, who might delay less than indigent married patients. The pattern of delay in those 65 years and older for once supports the possibility that the higher payment group believes more in the value of early rehabilitation and thus delays less than the indigent group.

Using the side of disability and the disability score on admission as measures of the severity of disablement, it appeared that the more disabled patients delayed longer than the less disabled. This finding was the reverse of that expected since the most disabled patients were the greater burdens on their relatives and should have delayed less. A possible explanation for this reverse finding may be that slower applicants had more time to deteriorate, and that their greater disability was the result of their long delay rather than a causal factor in it. However, this

does not explain why those with bilateral involvement delayed longer than those disabled on one side only, since bilateral involvement would cause greater disability from the onset of the stroke. An alternative explanation may be that those with severe disability stayed longer in acute hospitals, and that the application for rehabilitation was made only toward the end of the acute hospital stay.

We have thus found the short-delay applicant to be elderly rather than middle-aged, female rather than male, nonwhite rather than white, and widowed rather than married. These characteristics are all compatible with the hypothesis that socioeconomic problems, rather than a positive desire for rehabilitation, formed the major reason for seeking care. The typical short-delay applicant, if educated to the value of rehabilitation, would be young rather than elderly, white rather than nonwhite, married rather than widowed, and of either sex.

So far, I have not pointed out that a hospital rule was responsible for a small part of the delay. The families of patients were required to visit the Welfare Department, an agency associated in the public's mind with indigency and charity, for financial certification before the application was made. This requirement was changed in 1959. Nor have I mentioned the obvious fact that personal physicians cared for the applicants, and that these physicians must have had some influence on the delay in seeking rehabilitation. That 25 per cent of this study group delayed more than 50 weeks before applying for such care suggests that patients with CVA, their families, and, perhaps, their physicians need to be convinced that early rehabilitation has value. It seems true that ". . . in the whole field of Physical Medicine and Rehabilitation there is too much emphasis on method and too little on the results obtained with these methods . . ."[11] Adequately controlled studies of the results of rehabilitation may overcome the pessimistic prognosis given to patients with CVA. Moreover, the philosophy must spread that long-term patients, whether old or young, deserve the same interest and the same vigorous standards of care as we demand for short-term patients. It should no longer be acceptable to give custodial care to the hemiplegic patient if rehabilitation is possible.

Delay in seeking adequate care is a wide problem which involves more than just the patient, his family, and his physician. Community attitudes must be examined to translate this study into corrective action. We must know how the public defines a stroke, and what its expectations are concerning the stroke and rehabilitation; these findings must then be compared with the expectations of physicians. Similarities and contrast will expose the true factors responsible for delay. Should the physicians have the "correct" attitude, they may be failing to communicate it because of a deeply ingrained pessimism in the patient and family; or the physicians themselves may be transmitting the pessimistic attitude. Such data must guide the direction of future programs aimed at reducing delay.

SUMMARY

In this study of delay in seeking rehabilitation for hemiplegia, we used the data on the application forms for 612 patients with CVA who applied to a rehabilitation center in Maryland. Short delay in applying was associated with

those 75 years and older, females, nonwhites, and those without a living spouse. The findings by income group were less consistent. Long delay in applying was associated with severe disability on admission, although the findings were not conclusive. The pattern of delay was compatible with the hypothesis that socio-economic problems, rather than a positive desire for rehabilitation, formed the major reason for applying for care. A study of the physician's and the community's attitudes towards strokes and rehabilitation is needed to supplement this study and to assist in the direction of programs aimed at reducing delay.

Miss Betty White, A.M.R., and Mrs. Janet Hare, assisted in collecting data for this study. I gratefully acknowledge the help of the Montebello Hospital staff, who allowed me free access to all medical records.

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Rehabilitation

PSYCHOLOGICAL REMOTIVATION OF THE CHRONICALLY ILL MEDICAL PATIENT: A QUANTITATIVE STUDY IN REHABILITATION METHODOLOGY

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THIS project was designed to study in the hospitalized medical patient with chronic disease the psychobehavioral effects of a comprehensive program of rehabilitation which applies all pertinent paramedical modalities and includes nursing service, recreation, occupational therapy, manual arts therapy, corrective therapy, chaplain services, library, volunteer services, music therapy, social services, and psychology.

Recent investigations[1-4] have suggested that the comprehensive and intensive rehabilitation type of approach to the older, long-institutionalized or long-hospitalized patient has an important influence in motivating him to utilize those potentialties which remain to him. Long-continued disease and long hospitalization, continued isolation from the normal stream of ongoing human affairs, restrictions imposed upon the bedridden or the hospital-bound person, and passivity with a decrease of interest in the environment—all these have a profoundly adverse psychological effect upon the hospitalized patient. This is especially so for the older patient who is in the danger zone for emotional and psychosocial deterioration just as he is for physical deterioration. The desire for pleasure and for social interaction, the motivation to *do* and to take advantage of available enjoyments, the wish to care for one's self to the best of one's ability—all these suffer.[5]

The supervisory physician who is in charge of the medical wards for the chronically ill patients in a 1,005 bed general hospital under the Veterans Administration requested that a program be developed to assist in the psychological remotivation of these older, chronically ill medical patients who had been hospitalized for extended periods of time. A research investigation was therefore

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designed and conducted to evaluate the effectiveness of a program of psychological remotivation with hospitalized, chronically ill medical patients.

Psychological remotivation in this experiment is defined as follows: (1) recovered or improved mental state of happiness, comfort, feeling of well-being, (2) increased willingness to communicate with the environment, and (3) increased utilization of the remaining potential assets in the self for activity and participation in the environmental milieu. It does *not* imply the goal of hospital discharge, or recovery to socioeconomic self-sufficiency. Operationally, it is defined in terms of the instruments of measurement described below.

SUBJECTS AND MATERIALS

The service for chronically ill medical patients, all male, was comprised of three wards. One of these, a ward of 39 patients, was selected as the experimental group or ward. This group was matched with a control group of 14 patients from a second ward for chronically ill medical patients. These groups were matched as closely as possible on the basis of educational level and behavioral adjustment to the ward. The control group was necessarily smaller in size because of the difficulty in matching its characteristics to those of the experimental group.

The patients of the experimental group had a mean age of 62 years, mean educational level of 7.9 years, mean frequency of 2.25 previous hospitalizations, and had been hospitalized continuously for a mean of 2.4 years for this particular hospitalization. The patients of the control group had a mean age of 68 years, mean educational level of 7.8 years, mean frequency of 2.4 previous hospitalizations, and had been hospitalized continuously for a mean of 1.3 years for this particular hospitalization. It is most important that the initial behavioral adjustment to the ward and the morale were closely similar for both groups as measured by the behavioral rating scale scores (Table II, "Pre" column) and structured attitude interview scores (Table IV, "Pre" column).

Various conditions had been diagnosed in these chronically ill medical patients: lung and chest diseases (but not active tuberculosis), cardiac, vascular, and metabolic disorders, malignancies, and several cases of degenerative nerve diseases (nonpsychotic).

Three instruments of measurement were employed to compare the state of morale of the experimental and control patients and these patients' psychological motivation to utilize fully (within the hospital) their remaining physical and mental assets.

Behavioral Rating Scale.—This was a shorter version of a 100 item scale previously developed to measure the social communication and ward adjustment of hospitalized, chronically ill psychiatric patients. Its scoring reliability by correlation coefficients was 0.79 and higher. The scale showed high validity by t test and by chi square test of independence in its ability to differentiate behaviorally well-adjusted from behaviorally poorly adjusted chronically ill patients (level of confidence $p < 0.001$).[6] For present use, those items were omitted which pertained only to psychiatric patients, as, for example, the presence of hallucinations or delusions or obscene behavior. The other 81 items of the scale were short, concrete, easily readable, and could be answered "yes" or "no" by the rater

(in this case, the nurse in charge of the ward). They covered five major areas: self-care, orientation, communication and socialization, cooperation, and reaction to environment. Examples of item content were: "patient makes his own bed," "mixes with other patients," "likes to change his clothes," and "writes letters." Total rating time per scale was under 5 minutes. Ratings on experimental and control patients were made by their respective ward nurses according to a specified time schedule. Each item rated in the direction of a healthy adjustment received a weight of 1; 81 was the highest possible total score.

Structured Attitude Interview Schedule.—An individual questionnaire survey interview was conducted with each patient by a clinical psychologist. This interview schedule explored the patient's feelings about his ward, his treatment, the professional personnel of the hospital, and the progress he thought he was (or was not) making. There were 10 items in all, and the response of the patient was scored on a graduated scale from low (poor morale) to high (good morale). The items were simple, concise, and minimized interpretive inference on the part of the interviewer. Whenever possible the questionnaire was filled in directly by the patient while the interviewer was present and available to answer questions or clarify the meaning of the items. Scores which ranged from 0 through 3 were assigned to responses to the item; the higher the score, the higher the indication of morale. The maximum possible score on this instrument was 28.

Activity Participation.—Each patient was scored for the total number of different institutional activities in which he regularly participated on a weekly basis. The frequency of recurrence of the activities varied from a maximum of once per day to a minimum of once per week. For example, group psychotherapy occurred 5 times per week; travel outings, once per week; occupational therapy, 5 times per week; ward work assistance, which included carring trays and/or running errands, daily. The count was in terms of the number of types of different (but recurrent) activities in which the patient engaged each week. Hence, an index of 1.00 would mean one activity per week irrespective of its frequency of recurrence within that week. The time devoted to any individual activity session was a minimum duration of 1 hour per session. Basically, therefore, this was a numerical count of recurrent types of activity in which the patient engaged per week in which the duration of the individual session was of one or more hours. It excluded, of course, those purely functional activities in which all engaged, such as eating, sleeping, and merely moving about the ward. The activities were classified into two major categories: (a) voluntary activities—those which were available to the patient for his participation but which he was not required to attend, for example, church services, hobbies, daily chores, and outings; and (b) involuntary activities—activities and rehabilitation therapies which he was required to attend, for example, group psychotherapy, educational therapy, manual arts, and music group. The patient's total activity participation score, therefore, consisted of three parts: the total number of different activities in which he regularly participated per week, and this total subdivided into the voluntary and the involuntary activities. The number of voluntary activities attended was essentially an index of his outwardly directed interests and/or

energies—the degree to which the patient directed *himself* into the social and recreational activities available to him in his environment. The number of involuntary activities attended was an index of the number of activities and therapies which were forcefully provided by his milieu and which he attended. Despite administrative pressure to attend the involuntary therapies, the patients did exert a certain amount of selection through resistive techniques, such as failure to attend, "conflicting appointments," and lateness. This psychological distinction between voluntary and involuntary activities provided sufficient reason to make separate analyses of each type, as well as an analysis of the total number of activities both types combined.

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PROCEDURES

The project was run for 16 weeks and had three measurement intervals. The first measurement (pre, basal) was taken prior to the experiment (first week in October); the second (mid) was taken 8 weeks later (first week in December); and the third (terminal) was taken 8 weeks after that. All three measurement instruments were employed at each of these intervals. The basal scores gave the patients' status prior to the beginning of this project, their behavioral adjustment on the ward, their general morale, and the degree of their participation in activities. The mid scores, centrally within the program, revealed the progress, if any, which had been made within the brief period of 8 weeks. The terminal scores reflected the over-all progress, or lack of it, and pointed up any accrual or loss during the second 8 week interval of the project.

All the activities that were customarily available for rehabilitation and recreation were accented and applied as intensively as possible to our experimental group. No additional staff personnel was hired, although we used all resources which were available in the hospital for our experimental group. A clinical psychologist on the experimental ward served as coordinator and consultant for the program. Biweekly meetings were held with the immediate ward personnel (nurses, aides, physician, and social worker) to resolve administrative problems and to discuss the progress of the individual patients. Decisions about new treatments, discontinuation of treatments, and the necessary changes of attitudes or approach to the patient were all considered here. Weekly meetings were also held with the personnel concerned with rehabilitation. Participants in this project were from manual arts; occupational, corrective, and educational therapies; physiotherapy; social service; chaplains; librarian; recreational therapy; volunteer activities; clinical psychologist; and the personnel of the ward such as physician, nurse, and aide. Group psychotherapy was provided for all patients in the experimental group. The personnel in the nursing service had been informed of the program and were cooperative to the fullest extent, as were all participants. We tried to keep the ward "climate" friendly and socially pleasant. Group staff meetings were oriented toward motivating the personnel of the staff to exert their utmost energies for the patients. We attempted to improve the attitudes of the staff concerning work with chronically ill patients. We tried to create a better feeling tone and morale on the part of the staff itself.

RESULTS

The number of patients in the experimental group who were initially entered in this project was 39 and remained so for the duration. The control group, which numbered 14 initially (basal), was smaller in size due to difficulty in matching with the experimental group. The control group numbered 13 at the 8 week evaluation (mid) and 11 at the 16 weeks' (terminal) evaluation. Three patients were lost from the project, two because of transfer and one because of serious intercurrent illness. All mean scores reported hereafter for the different evaluative techniques (behavioral rating scale, structured attitude interview survey, and activity participation) are, therefore, based upon Experimental Group N = 39 and Control Group N = 14 initially, Experimental Group N = 39 and Control Group N = 13 at 8 weeks, and Experimental Group N = 39 and Control Group N = 11 at 16 weeks. When tests of statistical significance were made for the *same* group from one rating interval to another, the formula for matched pairs was used to decrease variance and sharpen significance. In the control group this necessitated certain recomputations in accordance with the altered size of the sample. In these instances the reported means are for the full control sample at each rating period, but the reports of the *t* test with their corresponding probabilities are based upon the corrected size of the sample in accordance with the formula for matched pairs. The correction had a negligible effect upon mean scores.

Behavioral Rating Scale.—Table I reports the mean scores of the behavioral rating scale for the experimental and control groups at the three rating intervals. It presents the statistical significance of the respective changes (differences) in these mean scores over the course of the several rating intervals.

TABLE I. MEAN SCORES ON THE BEHAVIORAL RATING SCALE FOR EXPERIMENTAL AND CONTROL GROUPS

RATING PERIODS COMPARED	MEAN SCORES					
	EXPERIMENTAL GROUP	DIFFERENCE	p	CONTROL GROUP	DIFFERENCE	p
Pre (basal) versus 8 weeks (mid)	48.64 (N = 39) 53.41 (N = 39)	4.77*	.02*	46.86 (N = 14) 38.69 (N = 13)	−8.17	.30
8 weeks (mid) versus 16 weeks (terminal)	53.41 (N = 39) 56.69 (N = 39)	3.28	.30	38.69 (N = 13) 45.54 (N = 11)	6.85	.40
Pre (basal) versus 16 weeks (terminal)	48.64 (N = 39) 56.69 (N = 39)	8.05*	.001*	46.86 (N = 14) 45.55 (N = 11)	−1.31	.80

*Statistically significant difference at the indicated probability level p.

The experimental group made a significant gain (8.05 score points) during

the 16 week course of the project ($p = 0.001$). The major portion of that gain was made within the first 8 weeks. By contrast, the control group showed a slight but nonsignificant total loss of 1.31 points from the pretest to the terminal phase. Within the first 8 weeks there was an even greater but still nonsignificant transitory loss, followed in the second 8 weeks by recovery close to the initial level as indicated in Table I.

Table II reports the significance of the mean difference between the experimental and control groups at each of the three rating intervals. The two groups were initially equivalent at the time of the Pretest (basal). By the eighth week the experimental group had attained significant superiority over the control group. This superiority was retained through the ensuing 8 weeks although not to the same extent.

TABLE II. COMPARISONS OF MEAN SCORES ON THE BEHAVIORAL RATING SCALE FOR EXPERIMENTAL AND CONTROL GROUPS

GROUPS COMPARED	RATING PERIODS		
	PRE (BASAL)	8 WEEKS (MID)	16 WEEKS (TERMINAL)
Experimental Group Mean Score versus Control Group Mean Score	48.64 / 46.86	53.41 / 38.69	56.69 / 45.55
Difference	−1.78	−14.72*	−11.14*
p	.70	.01*	.05*

*Statistically significant difference at the indicated probability level p.

The numerical results described in Tables I and II are graphically presented in Fig. 1. The experimental group improved significantly, the control did not.

It will be recalled that the 81 items of the behavioral rating scale were subsumed under 5 major categories of behavior: self-care, orientation, communication and socialization, cooperation, and reaction to environment. Chi square tests were conducted to test the hypothesis that the improvement in the experimental group was differential in the sense that one or two of these major categories showed relatively more improvement than the others. The results were distinctly negative and the hypothesis was therefore rejected. No single area gained significantly more than the others. The improvement in behavioral adjustment to the ward was equitably distributed among all 5 of these major categories of behavior.

Structured Attitude Interview Survey.—Table III reports the mean scores of the attitude survey for the experimental and control groups at each of the three rating intervals. It presents the statistical significance of the changes in each group at each rating interval. The experimental group made a statistically significant gain of 6.41 points within the full 16 weeks ($p = 0.001$). The greater

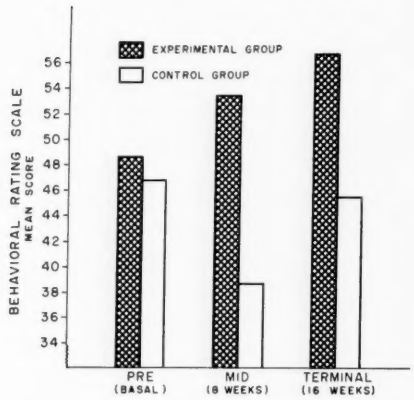

Fig. 1.—Behavioral rating scale scores of experimental and control groups.

portion of this was accrued during the first 8 weeks. The control group gained a smaller total of 2.70 points, which, however, was also statistically significant at a lesser probability level ($p = 0.05$). The greater portion of this gain was made in the second 8 week period.

TABLE III. MEAN ATTITUDE SCORES FOR EXPERIMENTAL AND CONTROL GROUPS

RATING PERIODS COMPARED	MEAN SCORES					
	EXPERIMENTAL GROUP	DIFFERENCE	p	CONTROL GROUP	DIFFERENCE	p
Pre (basal) versus 8 weeks (mid)	17.24 (N = 39) / 22.70 (N = 39)	5.46*	<.001*	18.07 (N = 14) / 18.88 (N = 13)	0.81	>.90
8 weeks (mid) versus 16 weeks (terminal)	22.70 (N = 39) / 23.65 (N = 39)	0.95	.90	18.88 (N = 13) / 20.77 (N = 11)	1.89	.20
Pre (basal) versus 16 weeks (terminal)	17.24 (N = 39) / 23.65 (N = 39)	6.41*	<.001*	18.07 (N = 14) / 20.77 (N = 11)	2.70*	.05*

*Statistically significant difference at the indicated probability level p.

Table IV shows the results of difference (t-) tests between the mean scores of the experimental and the control groups at each rating period. The two groups were initially equivalent, but by the eighth week the experimental group was significantly superior to the control group. This superiority was retained throughout the remaining 8 weeks. The total gain of 6.41 points by the experimental group was significantly greater ($p = 0.003$) than the total gain of 2.70 points by the control group. Fig. 2 portrays graphically the findings reported in Tables III and IV.

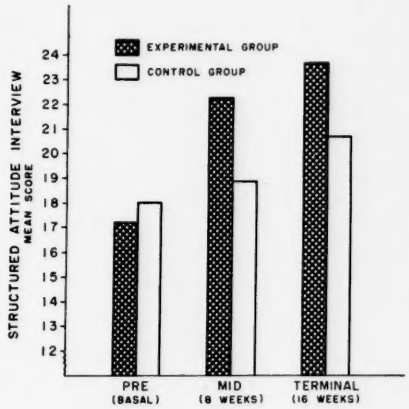

Fig. 2.—Structured attitude interview scores of experimental and control groups.

TABLE IV. COMPARISONS OF MEAN ATTITUDE SCORES FOR EXPERIMENTAL AND CONTROL GROUPS

GROUPS COMPARED	RATING PERIODS		
	PRE (BASAL)	8 WEEKS (MID)	16 WEEKS (TERMINAL)
Experimental Group Mean Score versus Control Group Mean Score	17.24 / 18.07	22.70 / 18.88	23.65 / 20.77
Difference	0.83	−3.82*	−2.88*
p	.60	.001*	.003*

*Statistically significant difference at the indicated probability level p.

In recapitulation, morale and the feeling of mental well-being as measured by the structured attitude interview schedule improved significantly more for the experimental than for the control patients.

Activity Participation.—Tables V and VI report the mean scores for voluntary, involuntary, and total activity participation at each measurement interval for the experimental and control groups, respectively. The sequential changes with time for each group were tested for statistical significance, and the results of these tests are given in the tables. Table VII compares the mean scores for activity participation between the experimental and control groups at each measurement period, and reports the significance of the differences between their means at each of the three periods. Fig. 3 visually represents these several findings for activity participation.

Prior to this investigation both groups were participating in all activities to approximately the same degree (Table VII, basal comparison). Although the

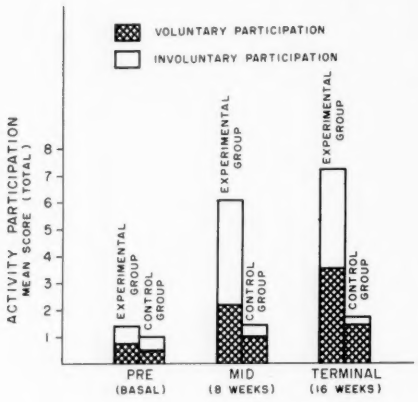

Fig. 3.—Activity participation scores of experimental and control groups.

experimental group had slightly higher initial mean participation scores than the control group, this was well within the limits of chance and not a statistically significant difference.

The control group, when compared with itself later showed some increase in voluntary activities from basal to mid tests (Table VI, Voluntary: $p = 0.05$) and from basal to terminal (Table VI, Voluntary: $p = 0.02$). However, the experimental group showed much greater increase, at higher significance levels, and in more areas (Table V). When the experimental group was compared with the control group (Table VII), it was evident by the eighth week that the experimental group had attained a statistically significant degree of superiority over the control group for voluntary, involuntary, and total participation activities. They maintained and increased this superiority throughout the duration of the project. This signified that the experimental patients were now being offered many more activities, that they were participating in these activities significantly more often, and that they voluntarily sought out more of the available activities even when not required to do so by the hospital staff.

DISCUSSION

The experimental group showed a significant gain over the control group by all three methods of evaluation: behavioral ward adjustment, structured attitude interview survey, and activity participation scores. The increase in voluntary activity participation by the patients was more meaningful for our thesis of psychological remotivation than was their increase in involuntary activity participation. The latter was, perhaps, but a mechanical consequence of the greater treatment time expended by the staff, whereas the former reflected behavioral changes which resulted from a heightened and introjected remotivational force which was integrated into the inner personal regions of the self and emerged as observable behavior.

One weakness of this study lay in its smaller number of control patients. It would have been advisable to raise the number by including control patients from other wards for chronically ill medical patients within the hospital.

TABLE V. MEAN SCORES FOR ACTIVITY PARTICIPATION OF EXPERIMENTAL GROUP

RATING PERIODS COMPARED (EXPERIMENTAL GROUP)		VOLUNTARY			INVOLUNTARY			TOTAL		
		MEAN	DIFFERENCE	p	MEAN	DIFFERENCE	p	MEAN	DIFFERENCE	p
Pre (basal)	N = 39	0.79	1.36*	<.001*	0.64	3.28*	<.001*	1.43	4.64*	<.001*
versus										
8 weeks (mid)	N = 39	2.15			3.92			6.07		
8 weeks (mid)	N = 39	2.15	1.36*	<.001*	3.92	−.20	.60	6.07	1.16	.30
versus										
16 weeks (terminal)	N = 39	3.51			3.72			7.23		
Pre (basal)	N = 39	0.79	2.72*	<.001*	0.64	3.08*	.001*	1.43	5.80*	<.001*
versus										
16 weeks (terminal)	N = 39	3.51			3.72			7.23		

*Statistically significant difference at the indicated probability level p.

TABLE VI. MEAN SCORES FOR ACTIVITY PARTICIPATION OF CONTROL GROUP

RATING PERIODS COMPARED (CONTROL GROUP)		VOLUNTARY			INVOLUNTARY			TOTAL		
		MEAN	DIFFERENCE	p	MEAN	DIFFERENCE	p	MEAN	DIFFERENCE	p
Pre (basal)	N = 14	0.50	0.50*	.05*	0.50	−0.04	.70	1.00	0.46	.10
versus										
8 weeks (mid)	N = 13	1.00			0.46			1.46		
8 weeks (mid)	N = 13	1.00	0.45	.30	0.46	−0.10	.40	1.46	0.35	.50
versus										
16 weeks (terminal)	N = 11	1.45			0.36			1.81		
Pre (basal)	N = 14	0.50	0.95*	.02*	0.50	−0.14	.40	1.00	0.81*	.05*
versus										
16 weeks (terminal)	N = 11	1.45			0.36			1.81		

*Statistically significant difference at the indicated probability level p.

TABLE VII. COMPARISONS OF PARTICIPATION SCORES FOR EXPERIMENTAL AND CONTROL GROUPS

	GROUPS COMPARED	VOLUNTARY ACTIVITIES			INVOLUNTARY ACTIVITIES			TOTAL ACTIVITIES		
		MEAN	DIFFERENCE	p	MEAN	DIFFERENCE	p	MEAN	DIFFERENCE	p
Pre (basal)	Experimental Group	0.79			0.64			1.43		
	versus		−0.29	.30		−0.14	.70		−0.43	.30
	Control Group	0.50			0.50			1.00		
8 weeks (mid)	Experimental Group	2.15			3.92			6.07		
	versus		−1.15*	.001*		−3.46*	.001*		−4.61*	.001*
	Control Group	1.00			0.46			1.46		
16 weeks (terminal)	Experimental Group	3.51			3.72			7.23		
	versus		−2.06*	.01*		−3.36*	.001*		−5.42*	.001*
	Control Group	1.45			0.36			1.81		

*Statistically significant difference at the indicated probability level p.

A possible source of experimental error lay in the fact that ratings and evaluations were made by personnel who knew which patients were in the experimental and which in the control groups. It was common knowledge of the staff that the experimental ward was the focus for a program of remotivation. Since the ward and rehabilitation personnel were key figures in such an activation process, it was necessary that they be drawn fully into the total remotivation focus. The behavioral ward adjustment ratings employed in this project demanded intimate knowledge of the patients. It was therefore inevitable that the nurse who rated the patient's behavioral adjustment to the ward also be aware of that patient's inclusion within the remotivation project. In a study such as this, it is not inconceivable (although improbable, in our opinion) that the participating personnel, for example, the nurse who made the ratings of behavior, could have been so imbued with enthusiasm and positive satisfaction by the project that through a process of selective misperception the patient was rated as improved behaviorally despite an objective *no change* in true adjustment. The type of concrete and simple rating scale employed here,[6] based upon actual bits of behavior rather than inferred judgments, rendered such misperception unlikely. But, as a theoretical source of error, it constitutes a possibility and, ideally, should be mitigated by the accessory use of methods not open to this error, as, for example, objective psychological tests which could be scored in the absence of knowledge as to the experimental or control status of the patients within the project. The structured attitude interview survey, ideally, should also be conducted by a "stranger" interviewer brought in for this alone and without any knowledge of the experimental or control status of the patients under review. This would, of course, raise an alternative problem: the patient's willingness to relate himself to a stranger, his willingness to reveal to the stranger his inner thoughts and his critical reactions concerning the hospital regimen. The activity participation scores were a numerical count index and, therefore, refractory to the error of bias in judgment which is under discussion here.

This experimental project did show a remotivating effect upon the experimental group according to the criteria employed. No additional personnel were brought into the hospital to accomplish these results and the only administrative change was constituted by the presence of a clinical psychologist who served as coordinator and consultant for the experimental ward. Clinical psychological service had been and continued to be available to the control ward, as it was for all medical patients before and during this study, but such service was requested infrequently and mainly in connection with special problems of diagnosis or discharge. It was certainly true that the medical, rehabilitation, and recreational staffs gave more interest and probably more time to the patients in the project, but this enthusiasm and time were not at the expense of other patients. It was "found" time—time over and above that ordinarily given to the care of patients.

The presence of the clinical psychologist as coordinator-consultant on the experimental ward was most important to the positive findings of this study. His enthusiasm and persistent effort in discussions with the staff on the ward, his pinpointing of weaknesses with suggestions for their remedy, his coordination of the programs of the experimental ward, his attention and encouragement to

the staff and to the patients, his very physical presence as a symbol and reminder—all these were instrumental in remotivating the patients and enhancing the staff's efforts. We do not believe it necessary that such a role be limited to any one profession; various professions might prove fully as effective as coordinator-consultant, for example, a social worker or psychiatrist or medical physician. What is more important is that the coordinator-consultant be enthusiastic and energetic in his efforts and have an understanding of human relationships which he applies in his work with the staff and patients.

It might be argued by some that the presence of a coordinator-consultant on the experimental ward and his concomitant absence on the control ward vitiates these findings. This is by no means true. It is precisely this type of differential effort, together with other previously specified differential factors, which makes—and did make—the difference in remotivational response between the experimental and control patients over the course of the study. No one therapeutic or recreational endeavour can be pinpointed as the main cause of improvement in these patients. All the pertinent staff members carried out their roles and worked together and separately to attain the final outcome of remotivation. The design of this study does not permit the factoring out of the "remotivational power" of any one therapeutic modality, as, for example, of group psychotherapy per se or of occupational or music therapy alone. It might be possible to design a type of study which would reasonably permit measurement of that remotivational quantum which accrued from one or two specific types of treatment, but to devise a method for the factoring out of the specific and differential effects respectively of nursing care, group psychotherapy, recreational activities and outings, ward work and errands, music therapy, occupational or manual arts therapy, volunteer visits, etc., requires methods and approaches, which, if possible at all, are far beyond the scope of the present type of study. A complicating factor, when one studies the therapeutic efficacy of any one of these modalities, lies in the broad continuum of bipolar attitudes of the staff which may accompany that modality. For example, if music therapy is widely accepted and approved by the hospital staff, then the music therapist will find an enhanced receptiveness in his patients for the kind of therapeutic endeavors which he can provide: music in its several active and passive forms for participation. If it is regarded as an unnecessary frill, then this will be communicated to the patients who will accordingly respond in negative fashion. Or, music therapist A might be a flexible, warm, socially mature, and knowledgeable individual concerned with the patient's personal and social growth through the vehicle of music, whereas music therapist B might be rigid, socially distant, and relatively more concerned with the forms of music than with the patient's personal and social growth through that vehicle.

These complications are, of course, present whether one studies the therapeutic efficacy of any one treatment method for rehabilitation or the remotivational power of all the methods combined and integrated, as in the present report. Nevertheless, it is precisely here, where one considers the attitudinal climate of the hospital as it is mirrored in the interpersonal reactions of the staff to the patients, that the greatest value from intensive effort, as described here, accrues to the chronically ill patient.

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The remotivation of *patients* to carry forward in rehabilitation is but one aspect of the total problem. Fully as important, although we have adduced no direct quantitative findings in this report, is the motivation of the ward and rehabilitation personnel to exert themselves more fully in their work with these patients. It was our distinct impression that the remotivational effectiveness of this project depended in great part upon the attitude, interest, and mutual interchange among the rehabilitation and health personnel who provided the total treatment climate for these patients. Efforts toward remotivation involve the wholehearted participation of the personnel concerned with treatment. Much effort must be, and was, directed toward motivating and interesting the staff, since, in the final analysis, it is they who influence the patients; they, at all hierarchical levels from porter to physician. Qualitatively we observed a growth of enthusiasm and eagerness in the personnel who participated in this study. It was as if the research project itself lent importance and worthwhileness to the ongoing treatment of these chronically ill medical patients. In discussions with the nurses and resident physicians in the general hospital it was apparent that they had previously regarded the wards for the chronically ill medical patients as a kind of medical "Outer Mongolia" to which they were temporarily assigned and from which they sought early deliverance; a place where medical and nursing skills were not really used, hence, where the *raison d'etre* of physician and nurse was defeated. This research project, with its manifest demonstration of change and improvement in motivation and attitude of the patient, seemed thereafter to have had a positive influence upon the staff's view of work and service in the medical wards for the chronically ill patients. It had profound educative value along several dimensions. The drawing of the staff into a functional task group had positive influence upon staff morale. The focus of the group on patients tended to reduce interprofessional friction. The professional person's feeling of isolation from those patients who recover dramatically was lessened concurrently with the growth of feeling that one was participating in an important endeavor in rehabilitation. When improvement in the patient's remotivation occurred, it was communicated directly to the personnel. The process of education of the staff through group discussion of individual patients and their problems moved forward continuously.

Efforts toward rehabilitation as a continuing functional program can be incorporated into the milieu of hospital wards for patients with chronic diseases provided that appropriate attitudes are instilled into the social structures at the top or power echelons of the hospital. Projects and research programs, among other means, constitute an important channel for the dissemination of requisite attitudes and knowledge among the staff. Management and its administrative methods will set the ultimate limits: toward active rehabilitation if good, toward passivity if poor.

Why was there *any* improvement in the control patient group? One possible explanation lies in the coming of Christmas with its many attendant activities and the usual rise of gay holiday spirit within the hospital as a whole, which would, of course, influence the control patients, too. Again, the improvement might be reasonably attributed to a carry-over effect from the experimental to

the control ward. Both wards were part of the medical service for the chronically ill patients on the same floor of the hospital. There was informal communication between the personnel of both wards, especially nursing assistants, nurses, and physicians. Occasionally, a staff member of one ward had to cover some absence on the other ward. The same rehabilitation personnel were serving both wards. It is obviously impossible to maintain a rigid and artificial separation of wards or personnel in a hospital. Informal communication and carry-over effects must be expected, and, in fact, it is through such channels that one ultimately disseminates new knowledge and new enthusiasms for treatment. Finally, during this project 3 control patients were sent into a flurry of testing activities consequent upon a decision to bring them before the Medical Rehabilitation Board of the hospital for future planning. These 3 patients accounted for much of the increase in voluntary activity in the control group, as well as for some mean increase in the morale of the group. The heightened attention which they received while preparing for their presentation to the Medical Rehabilitation Board probably served to raise their own feeling of psychological well-being and their own motivation for participation in recreational and other activities.

In selecting patients for special emphasis on remotivation, as in this comprehensive program, should one choose those most likely to profit and most likely to make the greatest gains? This practical problem often confronts the rehabilitation worker. Given a specific or potential number of available man-hours of treatment, where will they make the greatest impact?

The problem is enormously complex and no single solution can apply in all cases. What constitutes "greatest gain" or "most likely to profit"?—absolute improvement? per cent improvement over initial status? discharge from the institution? A special chi-square analysis of the behavioral rating scale data for our experimental group indicated that the *per cent* improvement was as great for the patients with the lowest initial level of adjustment to the ward as it was for those with the highest initial level. In other words, the gain by the "poor risk" patients, (lowest level of adjustment to the ward) was *for them* just as great as the gain of the "best risk" patients (highest initial level of adjustment to the ward) was for *them*. From this standpoint, a small absolute degree of change in the one patient, the "poor risk" individual, is fully as significant as a large absolute degree of gain in another or "best risk" patient. Potentiality for improvement is *not* synonymous with initial level of adjustment or initial mental well-being As of this time there are no guideposts to tell us that such a one merits more (or less) endeavor in remotivation in terms of "pay-off."

Ethical considerations are perhaps most important of all in this connection. Who is to say that one patient is more worthy than another to receive the benefits of a comprehensive effort toward rehabilitation/remotivation? Our viewpoint on rehabilitation *compels* us to assist each patient to attain the maximum of his remaining potentialities, to make use of those capacities for enjoyment and for participation in the life which remains to him. Because he is old or because his disease is chronic and debilitating constitutes no ethical basis for the value judgment that we therefore de-emphasize his needs and turn our attention to younger patients or to patients with more dramatic conditions.

We must consider the hospitalized, chronically ill patient's own definition of his situation and life goals. Often he is afraid to leave the hospital and its protections and its aids. This was the case with many of the patients in our study. Hence, we set no arbitrary goal for them such as "discharge." Hospital discharge may or may not come later as a further development and consequence of the early stirrings introduced by this experimental program in remotivation. Indeed, had we implicitly or explicitly set this as an objective criterion of experimental success, then we might have occasioned much heightened total resistance within the patients. The research project set modest limits; the goals included ward adjustment, morale, and activities, rather than discharging the patient or making beds available. We were quite conscious of this point and held it before ourselves as a constant reminder.

If the patient were but newly admitted or only recently hospitalized, then discharge might be formulated for him as a major, immediate goal. In fact, these findings do underscore the need for instituting motivation and rehabilitation planning and action as soon as the patient enters the hospital setting, but they indicate further that it is never too late to begin such action, even after the passage of years.

What may we conclude from this experimental project? The greater the effort at remotivation and rehabilitation, the greater the results when measured in terms of the patient's feeling, morale, and adjustment. The motivation of the medical patient with a long-term illness to do for himself, to live more fully within the potentiality which remains to him, to participate in the ongoing life of his environment—all these are heightened by the increased interest and effort of the professional staff member directed toward the patient.

SUMMARY

The psychobehavioral effects of a comprehensive program of psychological remotivation directed to long-hospitalized, chronically ill medical patients were studied. The personnel of the hospital who had service responsibilities for the rehabilitation and treatment of these patients were drawn into the project.

Matched experimental and control groups were compared before, during, and at the end of a 16 week comprehensive attempt at psychological remotivation of the experimental group. Three measurement methods were employed for the comparisons: a behavioral ward adjustment scale, an activity participation index, and a survey of morale and attitudes. All 3 methods showed significant rise in superiority of the experimental over the control group through the full 16 week course of the research project. It was demonstrated that it was possible to remotivate those in this experimental group of chronically ill medical patients; this was manifested by their increment in healthier ward behavior, morale, and zest for living.

We wish to extend special thanks to the Hospitalized Veterans Service, Musicians Emergency Fund, Inc., for their donations of music equipment, music therapy time, and their technical assistance in implementing the music therapeutic rehabilitation aspects of this project. Wallace Kotter, Director of Special Projects, and Gladys Douglas-Longmore, Director, Hospital Program, were particularly helpful. Encouragement by Professor Robert P. Nenno and Dr. Thomas A. Gilmore is appreciatively acknowledged.

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Book Reviews

BEDSIDE MEDICINE. By I. Snapper, M.D. New York, 1960, Grune & Stratton, Inc. Pp. 592, indexed. Price $14.50.

Few people could have written this book. At an age when most physicians are coasting along on their laurels, Dr. Snapper has written a one-man textbook of medicine. For those who have seen Snapper in action on ward rounds, this volume will conjure up many memories. This reviewer remembers Snapper as an exciting teacher, at times the most charming of anecdote-tellers, at other times a *Geheimrat* who seemed to take fiendish pleasure in ripping an intern or resident to shreds (verbally, of course, although the effect was almost like physical punishment).

In *Bedside Medicine*, one also finds the fascinating anecdotes and the references to the medicine of other places and other times. There is, in addition, a great deal of solid medicine, since Snapper is more up to date than most internists 40 years his junior. But there are also occasional errors or opinions which will drive some experts into a frenzy. One recalls that Snapper has taught more than one house staff officer by forcing him to look up the literature to disprove some extravagant and outrageous-sounding "Snapperism." Dr. Snapper may relish such reactions, for all I know, but he certainly cannot purposely have erred so often in spelling or capitalizing drug names in his book, and the proofreading is as bad as I can remember in a book prepared by a major publisher. (On p. 351 one reads, for example, that ". . . axillary and public hairs are almost invariably absent in hypopituitarism . . ."; there are plenty of other such mistakes, albeit not as funny.)

Does the book deserve to be widely read? I think so. Dr. Snapper is a first-rate mind with unparalleled clinical experience. He is lucid and interesting, and has much to offer. Medical students might perhaps not be the best possible audience, but certainly any doctor can find much enjoyment in the pages of *Bedside Medicine*. Taking its title in a sense other than intended by the author, I finished the book by reading it a little at a time before retiring. Try it.

Louis Lasagna

SYMPOSIUM ON CORONARY HEART DISEASE. Edited by Herrman L. Blumgart, M.D. New York, 1961, The American Heart Association. Pp. 154, indexed.

This second American Heart Association monograph is a primer on coronary heart disease, and provides a reasonably good summary of the state of our knowledge as of 1961. The fifteen papers are written by well-known scientists, and while only one or two papers approach the level of the provocative and well-presented essay by Olson on diet and coronary artery disease, there are very few downright poor ones. The contributions on anticoagulants and amine oxidase inhibitors may strike some readers as a mite evangelical, but one other paper at least questions the conclusiveness of the data on anticoagulants. (And perhaps Griffith and Wright are not wrong in their enthusiasm.) While the sophisticated and well-read internist or cardiologist may not learn much from this monograph, certainly many other doctors and most medical students should profit by reading it.

Louis Lasagna

Announcements

The Francis Delafield Hospital, affiliated with Columbia University College of Physicians and Surgeons, New York City, is offering a THREE-YEAR RESIDENCY PROGRAM IN NEOPLASTIC DISEASES AND HEMATOLOGY accredited by the American Board of Internal Medicine.

The first year includes general medicine consisting of ward service, hematology, cardiology, and diagnostic radiology. The second year consists of training in either hematology or cardiology and supervision of first-year residents. The third year may be served as the Chief Resident or in a Fellowship program. Opportunity to do clinical and laboratory investigations are available during the second and third years.

The program can be started on July 1, 1962. The stipend depends on individual experience, with a minimum of $3,380. Living quarters, including meals, uniforms, and laundry privileges are provided in the hospital.

Applications should be addressed to: Alfred Gellhorn, M.D., Director of Medicine, Francis Delafield Hospital, 99 Fort Washington Ave., New York 32, N.Y.

In view of the rapid expansion which is forecast in the use of nuclear energy, x-rays, and other sources of radiation, a greatly expanded program for RESEARCH GRANTS IN THE FIELD OF RADIOLOGICAL HEALTH has been developed. These grants are offered to support research by individuals, universities, hospitals, laboratories, and other public or private institutions in the assessment and control of man-made and natural radiation exposures to the individual, no matter how the separate components may originate. The knowledge and skills of many professional disciplines and specialties—physicians, engineers, physicists, chemists, educators, statisticians among them—are needed to find answers to the many challenging questions in radiologic health.

Research proposals should contribute to the determination of the extent and character of the radiation problem as well as the mechanisms by which radiation produces damage. Studies aimed at the elucidation of the radiation damage "cause and effect" relationship are essential if low-level and long-term radiation exposure effects are to be accurately assessed and general control programs organized. Therefore, basic studies relating to critical body organs and systems, preferred metabolic pathways for specific radioactive contaminants, and an understanding of the radiosensitizing and modifying effects of various materials are encouraged.

Broad epidemiologic studies aimed at a scientific evaluation of the long-term effects such as aging, congenital malformations, genetic effects, behavioral patterns, and cancer induction are also of primary concern. Field studies of the movement of radioactive contaminants in biota and human food chains are of special interest, since we know the physical environment may be greatly altered by biologic activity, as for example, the concentration of waterborne radionuclides in microorganisms and fish.

Purely physical studies, such as chemical mechanisms in radiation chemistry, the design of equipment and the development of techniques to accurately assess or reduce the population dosages are mandatory for a successful research program.

Studies aimed at directing scientific findings toward control devices or procedures are necessary in a "total view" of man's ecologic system, as are studies that attempt to assess the relationship between health hazards created and possible benefits derived by radiation usage. The determination of the consequences of radiation exposure for present and future generations will require intensive investigation.

For information and/or application forms please contact: Dr. Paul F. Hahn, Chief, Office of Extramural Grants, Division of Radiological Health, United States Public Health Service, Washington 25, D. C.